

ESSENTIALS OF  
SYPHILOLOGY

FRONTISPIECE



Secondary syphilis—maculopapular rash.  
(Case 23.) (Kodachrome by T. S. Gibson )

# ESSENTIALS OF SYPHILOLOGY

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*87 Illustrations*

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*Dedicated to the Memory of*

J G R

*and*

C E M

*General Practitioners of Medicine*

## PREFACE\*

THIS book was prepared to provide a brief text on syphilis for the practitioner of medicine, since it seemed to me, after some years of conducting a short postgraduate course in this subject, that there was need for such a volume. The writing of this treatise has been undertaken in the face of the almost certain criticism of brevity and superficiality. However, I intend that it shall supply a practical exposition of syphilis as a systemic disease for the general practitioner, health officer, and undergraduate student. The objectives may be summarized as follows:

- 1 To present the concept of syphilis as a systemic disease whose manifestations may be manifold, at times presenting problems for every type of specialist, and thus perforce a disease of peculiar interest to the general practitioner

- 2 To promote better habits in history taking and physical examination on the part of the physician

- 3 To emphasize that, without exception in acute syphilis, a clinical diagnosis alone is not justifiable, but must be verified by either darkfield or serologic evidence of syphilis. (I say this advisedly, as the result of observing the too frequent willingness of the practitioner to advise treatment in nonsyphilitic patients incorrectly diagnosed.) This calls for less reliance on dermatologic diagnosis in early syphilis, but this is the only safe attitude to take

- 4 To develop a critical evaluation of serodiagnosis

- 5 To raise the index of suspicion as to the role syphilis may play in chronic disease years after infection was acquired

- 6 To stimulate better antisyphilitic treatment—especially its adequacy in early syphilis, and its more selective individualization in late syphilis

- 7 To show that the physician's responsibility in syphilis control does not cease when a patient having the disease is placed under treatment, and that a syphilitic patient represents merely one link in a long chain of infections. The physician must by himself, or through collaboration with the local health authorities, attempt to have examined (and treated, if

\* The following references may be of assistance to those interested in the teaching of syphilis:

Frye, W. W., R. H. Kampmeier, and A. E. Keller. The training of medical personnel in syphilis control, *Amer Jour Pub Health*, 32: 495, 1942

Kampmeier, R. H. The teaching of syphilis to undergraduates and postgraduates, *South Med Jour*, 31: 218, 1938

Kampmeier, R. H., and E. G. Clark. *Postgraduate course in syphilis control*, *Ven Dis Inform*, 20: 153, 1939

necessary) those contacts who may have been exposed to the patient during the infectious stage of the disease

8 Lastly, to demonstrate that the education of the patient relative to the disease is an important factor in the control programme

Certain limitations in the content of the book must be acknowledged. It is clearly recognized that the responsibility for a diagnosis of syphilis by darkfield examination in a seronegative lesion cannot be lightly shouldered by anyone with but little experience. It would be folly to go into this phase of diagnosis in such detail as to imply that a reading knowledge is all that is necessary to qualify the reader to undertake it.

The subject of serodiagnosis has been approached mainly from the viewpoint of interpretation of results. Those for whom this volume is intended have no hand in the performance of the tests. However, they must know what the reports of the tests mean. For this reason no space is given to the technic or details of the various tests. Any reader interested in these phases should consult one of the many good books on laboratory procedure.

To keep this volume within reasonable length, extensive discussion of differential diagnosis has been limited. Consideration has been given only to those dermatologic and systemic conditions which are common in the experience of the general practitioner. In the differentiation of the acute lesions of syphilis from other genital or skin diseases an attitude of certainty in clinical diagnosis has been avoided. In such instances, the practitioner can follow only one safe course, namely, the verification of a suspected diagnosis of syphilis by laboratory procedures. Obviously, there is no justification for lengthy discussion of conditions which might be seen but once in a physician's lifetime. Such discussions lead only to confusion, and becloud the issue. Paths indicated for further search in differential diagnosis will need to be followed in texts on dermatology, medicine, and neurology.

From five years' experience in postgraduate education in syphilis control came the realization that a certain dogmatism is essential in the presentation of the subject of treatment. This has been carried over into the discussions of therapy in the present treatise. No detailed consideration has been given to the management of those forms of neurosyphilis which involve the use of special forms of therapy. These require the advice of the consultant in neuropsychiatry.

The case reports, photographs, and certain of the data presented in this book have been taken from the material collected since 1925 in the Vanderbilt University Hospital. The recent introduction of a punch-card tabulating system has made readily available for statistical purposes 6,259 of the cases which have been studied in the Syphilis Clinic. In addition, there

have been many ward patients who have never been admitted to the Syphilis Clinic. Certain of the pathologic material as well as of the case abstracts presented in the book has been taken from this group of patients. Case abstracts have been used as examples to illustrate points in diagnosis, prognosis, and treatment. It has not seemed worth while to include case reports of rare manifestations of syphilis, even though available in our material.

Certain of my colleagues assisting me in the postgraduate course have contributed chapters on subjects which have fallen into their special field. These are the chapters on congenital syphilis and on the epidemiologic and preventive aspects of the disease.

Finally, the author makes no pretence to originality in the greater part of this volume. Unless one is a pioneer in a given field, one's practices are a compound of what has been read at various times, and then put into practice. Thus the findings and beliefs of the many become a part of the sum total of one's own experience.

R H K

NASHVILLE, TENNESSEE

## ACKNOWLEDGEMENTS

MANY more sources in the literature have been drawn upon than are indicated by the bibliography. The choice of bibliographic references has been influenced by the purposes of this book, and by the group of physicians for which it is intended. Thus the references have been almost exclusively limited to the American literature, and, when possible, to references in journals which are easily obtained.

In some sections of the book much use has been made of the Co-operative Clinical Group's findings, although with the realization that at best these probably represent a compromise by men of varied experiences and beliefs. In the absence of evidence to the contrary the author has been forced to accept, and pass on, some of the Group's findings.

In general, antisyphilitic treatment, as proposed by Dr J Earle Moore of Johns Hopkins University, has been the basis for the treatment plans used for many years in the Vanderbilt University Hospital Syphilis Clinic. His influence, therefore, will be obvious in the treatment schemes outlined in the book.

It was through the organization of the Syphilis Clinic at Vanderbilt University Hospital in past years by Dr Hugh J Morgan, Professor of Medicine and Head of the Department of Medicine, that we had the unusual opportunity to carry on teaching in this field. Because of his absence on active duty with the Army, it was impossible for him to review the manuscript of this book.

To Dr John B Youmans and Dr Edgar Jones, of the Department of Medicine, go my thanks for their great interest in, and for the time expended in the reading of, the manuscript. Their suggestions have been many, and of the utmost value.

Dr Waller S Leathers, Dean and Professor of Preventive Medicine and Public Health, has reviewed the chapters on the epidemiologic and preventive phases of syphilis. For this and his interest in the Syphilis Clinic I wish to thank him. Dr William W Frye has given worth-while advice in the chapters on prevention and control of syphilis.

Dr Horton R Casparis and Dr Katherine Dodd, of the Department of Pediatrics, have read the chapter on congenital syphilis, and have made valuable suggestions from their extensive experience in the field.

I am grateful to Miss Marie English, secretary to the Syphilis Clinic, for the typing of the manuscript, and for her assistance in the many details involved in the preparation of the material for this book. Thanks are due to Mr Homer Jones, photographer, for the illustrations which have been

included. Miss Anne Sweeney, of the Social Service Department, has assisted in the "follow-up" of some of the cases which have been used for their illustrative value.

And last but not least is my appreciation of the forbearance my wife has shown for the hours I have taken from my family in the preparation of this book.

R. H. K.

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# ESSENTIALS OF SYPHILOLOGY

## THE PROBLEM OF SYPHILIS CONTROL

THIS volume is dedicated to the memory of two general practitioners who represented the best type in this group of physicians. From the hours spent with the one in a rural mid-western "horse-and-buggy" practice came the stimulus to study medicine. From a pleasant association in general practice with the other came a viewpoint of the practice of medicine, since reinforced by several years of practice, which I hope has not been blunted by subsequent years in the medical school and teaching hospital. I prefer to think of this book on the subject of syphilis as one written by a general practitioner for the general practitioner.

With the rapid expansion of the syphilis-control programme in recent years, it quickly became apparent that, for geographic and economic reasons, most syphilitic patients must be treated by the general practitioner at the crossroads, by the part-time or full-time county health officer in the rural districts, and by the venereal-disease officer in the urban areas. Some idea of the extent of the expansion in the control of this disease may be obtained from the 1940 Annual Report of the Surgeon General of the United States Public Health Service. In the years from 1935 to 1940 the number of clinics reporting rose from 656 to 2,454, and the number of new cases of syphilis admitted to these clinics increased from 134,720 to 355,589.

Many syphilodermatologists believe that the management of syphilis should be in the hands of those especially trained in this field. It is at once obvious to the most casual observer that this is impossible for several reasons. Syphilodermatologists are too few in number to be able to care for all syphilitics. They are especially few and far between in those sections of the country in which syphilis is most frequent. In the South, for example, the prevalence of the disease among Negroes may be as high as 20-30 or more per cent. In rural counties where the population consists of 85 per cent Negroes, antisyphilitic treatment must be in the hands of the general practitioner or health officer. Furthermore, the vast majority of syphilitic patients are indigent or fall into the lowest income levels, and thus cannot afford a specialist.

Keenly aware of these facts, the United States Public Health Service, in collaboration with Vanderbilt University Medical School, established a short training course in syphilis control. This was planned for county

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health officers and private physicians co-operating with county health organizations, and for public health nurses

It has been the accepted belief at the Vanderbilt University Medical School that syphilis, by virtue of its widespread manifestations, belongs in the domain of internal medicine. The treatment of isolated lesions of syphilis by the specialist, in whose field the patient may at the moment belong, leads but to confusion. Therefore the Syphilis Clinic at Vanderbilt University Hospital is a special clinic in the Department of Medicine and cares for all patients with syphilis who are more than fifteen years of age. This applies irrespective of the manifestations of the disease, be they lesions of the skin, genitalia, eyes, viscera, bones, or central nervous system. In recent years another important activity has been added to the Syphilis Clinic the preventive and public health aspects of the disease. Thus emphasis has been placed on such things as epidemiology, contact investigation, and patient education.

This has been the clinic, then, in which we have conducted the short postgraduate courses in syphilis control. The personnel of our syphilis clinic has now had five years' experience in the conduct of such courses. After having given some two dozen courses within this time, a well rounded viewpoint of the needs of the general practitioner and the health officer in the satisfactory management of syphilis has been obtained. We have had the opportunity of evaluating the needs of men of all ages and of diverse schooling. Representatives of the medical and nursing professions from various parts of the United States, both urban and rural, have had this postgraduate work with us.

In addition to our evaluation of what the general practitioner and health officer needs, as determined in our course, we have amplified this information by a recent survey of the activities of the postgraduates after leaving our clinic. Such a survey has been carried out by questionnaire and visits by us in the field. The training they received is certain to have been reflected in the better management of the syphilitic patient. The extent of the influence of this training is indicated by the fact that 39 full time health officers who have taken the course are treating a total of 20,000 cases of syphilis weekly in 196 clinics.

With this background we have developed an opinion as to what knowledge is essential to the general practitioner or health officer for the diagnosis and treatment of the great majority of syphilitic patients.

From a clinical viewpoint the physician must think in terms of a systemic disease, which is almost always active and slowly progressive, and which may make itself manifest in one or more ways in any tissue of the body. He must discard a tendency to think of syphilis only in terms of disease of the genitalia or skin. His index of suspicion must be raised as to the

possible rôle of syphilis in chronic diseases appearing many years after the onset of the infection. The systemic characteristics of syphilis emphasize the need of proper history taking and physical examination.

The value and necessity of laboratory diagnosis in early syphilis must be stressed. Only the occasional recent graduate with good hospital experience may assume the great responsibility of making the diagnosis of syphilis by darkfield examination. However, the physician should know of the practicability of the darkfield examination in diagnosis and its great value in the early stages of the disease. (The survey of activities of our former postgraduates has shown that they are making use of the facilities for darkfield examination that have been made available to them by some public-health agencies.) The most important need of the practitioner is a knowledge of the place blood tests have in the diagnosis of syphilis—especially in early syphilis—and the interpretation of these tests in general.

In the field of therapy the physician must know what constitutes adequate treatment for a given stage of the disease, and the evils of under-treatment, especially in early syphilis.

Finally there must be awakened in the practitioner a sense of responsibility relative to the prevention and spread of the disease. Unless the physician attending a patient with early syphilis attempts to find and to treat the source of his patient's disease and to protect his patient's intimate contacts, he may need to assume the direct responsibility for other infections. The physician's informative instruction to the patient will enlist his assistance in bringing in exposed sexual partners and members of his family.

As was implied in the preface, it was our experience with the training of general practitioners and health officers in syphilis control, and a formulation of an opinion as to their needs, which led me to undertake the writing of this book. There is no thought that this volume will in the least supplant the extensive and detailed texts on clinical syphilology, on the treatment of syphilis, or on serodiagnosis. Such splendid texts are invaluable to the trained syphilologist. Nevertheless their use as reference books by the general practitioner, health officer, and undergraduate student is attended by certain difficulties. The volumes present so much and such detailed material that the nonspecialist is lost. He is confused by the exceptional cases cited in the clinical discussions, the highly specialized dermatologic descriptions of lesions, and the technical aspects of laboratory procedures. In general, the section on syphilis included in textbooks on dermatology stresses the dermatologic rather than the general field of syphilis. Though excellent descriptions of skin lesions are given, these represent but a passing phase of the disease, and insufficient space is given to the disease in its broader aspects. The average physician has been

found to have a fairly adequate knowledge of the diagnosis and treatment of acute syphilis. The problems of late syphilis and the stage of latency are those which trouble him most.

To the physician who is interested, syphilis offers an intriguing challenge to his diagnostic abilities, a satisfaction in the results of treatment in many of his patients, and an interesting insight into the psychological responses of his patients, for no other disease is related so deeply to fundamental emotions and instincts.

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## II

# THE BIOLOGY OF THE SYPHILITIC INFECTION

## HISTORICAL NOTE

### GEOGRAPHIC ORIGIN

MUCH has been written regarding the origin of syphilis, but discussion still continues as to its origin—whether it originated in the Old World or in the New. It is maintained by some that the disease was endemic in the Western Hemisphere, and that it was introduced into Europe by the men of Columbus' expedition. The main argument in favour of this viewpoint is that the disease was not recognized before this time, and that it became widespread throughout Europe immediately after this. In light of the slow communications of that age it is a remarkable epidemiologic fact that a disease should become so widespread in Europe within one year after the return of the men presumed to have been infected in the West Indies.

Pusey has been the strongest advocate of the American origin of the disease. He points out that it was described as being epidemic at the siege of Naples in 1494, one year after Columbus' return to Europe. It is presumed that the disease was brought to Italy by Spanish mercenaries in the army of Charles VIII of France. Pusey traces the spread of syphilis over Europe with the retreat of the French army from Italy. Evidence points to its appearance in France, Germany, and Switzerland in 1495, Holland and Greece in 1496, England and Scotland in 1497, and Hungary and Russia in 1499. At about these times the governments of certain European cities took recognition of the disease by establishing laws to prevent its spread. Thus laws banned prostitutes from some cities, and in others caused them to be branded. It is believed that syphilis was introduced to the Orient by Vasco da Gama's men who sailed from Portugal in 1497.

In Pusey's opinion, much importance is to be attached to the fact that no name was known in either the Occident or the Orient for this apparently new widespread disease. Several countries had their names attached to it, as the "French disease," "Spanish disease," etc. He emphasizes also that, like any other new disease introduced into a nonimmune population, it spread rapidly in epidemic proportions, and with severe clinical manifestations. After about fifty years the disease lost its severe characteristics, to assume those of syphilis of the present day.

The American origin of the disease is apparently borne out by the finding of supposedly unquestionable evidence of bone syphilis in the skeletons of American Indians dating back to about the year 1000.

The proponents of the Eurasian origin of syphilis feel that the varied manifestations of the disease were masked in the older literature by their inclusion in the clinical descriptions of leprosy. Many quotations have been brought forth,

from the period of the sixth century to the time of Columbus' return from America, to show that genital lesions were described which well might have been those of primary and secondary syphilis. Furthermore, it can be shown that the venereal nature of these lesions was known, and that recommendations were made with regard to prophylaxis after sexual exposure and the control of prostitutes. Those who favour the American origin of the disease will not accept these descriptions as being those of syphilis, but rather of other venereal diseases.

Nevertheless, the casual reader should not err in believing that the evidence for either origin is conclusive. The interpretation of descriptions of disease dating to the fifteenth and sixteenth centuries can be influenced too readily by the student's bias. There was much confusion relative to the identity of the venereal diseases up to even a century ago. The frequent descriptions and references at the beginning of the sixteenth century to the disease now accepted as syphilis, possibly can be explained (in part at least) by the recent introduction of printing. The name "syphilis" was applied to the disease by Fracastorius in a poem published in 1530, the name of the hero in the story being Syphilus.

#### RECENT HISTORY

The twentieth century saw the greatest advances in knowledge with regard to syphilis. Metchnikoff and Roux in 1903 successfully inoculated apes with infectious material. It remained for Schaudinn and Hoffmann actually to demonstrate the *Treponema pallidum* in 1905.

Although the organism of syphilis has been recognized during these several decades, much of the knowledge keenly desired about it is still hidden in darkness. The medical practitioner and student frequently are puzzled that much relative to the biology and immunology of the disease is still unknown. Several facts account for this, and an understanding of them will solve this bewilderment. Cultivation of the *T. pallidum* in artificial media is extremely difficult, in fact, there is a question in the minds of many whether the organism has ever been cultivated. The ape is the only experimental animal in which some phases of the clinical picture of the disease in man can be approximated. Obviously, expense and impracticability preclude extensive studies with this animal. In the rabbit, the animal commonly used in experimental work, the clinical course of the disease is not truly that as seen in man. Certain investigators have questioned the validity of some of the studies with this animal because of the possible complication of "rabbit syphilis," a genital infection due to *spirochaeta cuniculi* at times seen in rabbits.

Furthermore, protozoan (spirochetal) infection is not accompanied by recognizable humoral antibodies as is the case in bacterial diseases. Thus there are no opsonins, agglutinins, antitoxins, lysins, and the like. (Only very recently has Turner reported observations on humoral antibodies.) The complement-fixation and precipitation tests used in the serodiagnosis

of syphilis are not specific tests for the disease. The use of these tests, especially the precipitation test, in all warm-blooded animals other than man is open to question, since biologically positive tests in animals are common. Finally, certain knowledge relative to the course of the disease and the host's reaction is beclouded because syphilis does not kill early in the disease. Usually death occurs as the result of slowly progressing pathologic changes in certain vital organs many years after infection was acquired.

## THE ORGANISM

### MORPHOLOGY

The morphology of the spirochete of syphilis, the *T. pallidum*, can be studied best by darkfield examination of fresh material obtained from infectious lesions (Fig 1). It has a length of about 7-14 micra, although it may be longer, and is made up generally of 6-14 spirals, but may contain as many as 24. A single spiral is about 1 micron in length. In preparations from young lesions this anaerobic parasite is very motile, and may bend



FIG 1 *Treponema pallidum* (From Noguchi's material courtesy of Dr. Roy Avery, Department of Pathology, Vanderbilt University Medical School, and Jour. Exper. Med., June 1918.)

itself into shapes such as an O, C, V, etc. The movements of the *T. pallidum* are limited to three: corkscrew, backward and forward, and lateral flexion movements. Usually the spirals keep their uniform shape as related to each other, although very active treponemata may at times show an accordion-like opening and closing of the spirals. Organisms taken from some depth in acute lesions tend to be more active than those from superficial portions. (Only the spirochetes of yaws, bejel, and rabbit syphilis are morphologically indistinguishable from the *T. pallidum*.)

### BIOLOGY

The organism of syphilis cannot withstand drying. Its thermal death point is 114° F. *in vitro* for 7-10 minutes. In our laboratories it has been

kept at 46° F for several weeks without alteration of motility or virulence. Turner has frozen the organism and has kept it at -78° C. for a year. Upon being thawed, the organism was viable and virulent. In the serum from lesions of acute syphilis collected in capillary tubes and sealed with wax, we have demonstrated motility of the organism after seventy-two hours at room temperature. *T. pallidum* is killed in a few minutes by soap and water, and also by a 1:100,000 solution of mercury bichloride.

In their original papers, Schaudinn and Hoffmann commented upon the fact that, though the treponema was present in the acute lesions of syphilis, none could be found in the more extensive destructive manifestations of late or tertiary syphilis. Through the intervening decades much speculation has occurred concerning some as yet unknown change in the morphology of the organism at some stages in its life cycle. Thus various investigators have considered of significance the intracellular and extracellular granules which have been demonstrated at times in lymph nodes and in the late lesions of syphilis as a possible nonmotile stage of the *T. pallidum*. As is true of the spirochetes, these granules may be stained with silver. For the purposes of this volume, it is sufficient merely to point to such studies, and to indicate that it would be premature to attach too much significance to these findings.

The possibility of variations in strains of the *T. pallidum*, each having a predilection for invasion of certain body tissues—the cardiovascular system, the central nervous system, and the like—has often been raised for discussion. For the present, it may be said that no conclusive data have been presented in support of such a contention.

#### DISTRIBUTION OF THE *T. pallidum*

The parasite of syphilis spreads rapidly after invasion of the body at the site of inoculation. It may be demonstrated by darkfield examination under the following circumstances:

##### Primary Stage

- 1 In the papule which precedes the frank chancre
- 2 In the chancre
- 3 In the scar of the recently healed chancre of the untreated case
- 4 In the sentinel lymph nodes

##### Secondary Stage

- 1 In all the open and closed lesions, whether of the mucous membranes or skin.
- 2 In the apparently normal skin between cutaneous lesions
- 3 In the lymph nodes
- 4 In the lesions of mucocutaneous relapse

### Congenital Syphilis

- 1 In mucous membrane or skin lesions of syphilitic infants
- 2 In scrapings from the umbilical cord
- 3 In the liver and epiphyseal lines of bones

Astounding numbers of organisms may be found in the serum obtained from the surface lesions in acute syphilis. Vryonis and Morgan made counts of the number of organisms per cubic millimeter of serum obtained from fifty-three lesions in thirty-nine patients studied at Vanderbilt University Hospital. The results of their studies are summarized in Table I, taken from their report.

TABLE I

THE NUMBER OF "T. PALLIDUM" PER CU. MM. IN FLUID FROM THE LESIONS OF THIRTY-NINE PATIENTS WITH EARLY SYPHILIS\*

	Chancres <sup>1</sup>		Condylomata	
	"Active"	Epithelialized	Genital	Perianal
Number of lesions examined	9	3	14	4
Lowest count per cu. mm.	2,500	9,000	3,700	22,000
Highest count per cu. mm.	34,000	21,700	246,000	35,500
Average count per cu. mm.	14,900	14,400	40,200	28,600
		Moist	Moist	
			Lesions of	
			Recurrent	
			Early	
			Syphilis	
	Mucous	Extra-	Dry	(Mucocu-
	Patches	genital	Second-	taneous
	(Oral)	Skin	ary	relapse) <sup>3</sup>
		Lesions	Lesions <sup>2</sup>	
Number of lesions examined	5	6	6	5
Highest count per cu. mm.	37,400	9,200	3,200	24,800
Lowest count per cu. mm.	9,200	740	370	6,800
Average count per cu. mm.	24,700	4,500	1,800	11,700

\* Fluid from one neosarsphenamine-resistant chancre was examined. It is not included in this table. The treponema count was 370 per cu. mm.

<sup>2</sup> Healing extragenital ulcerations, extragenital papules and annular lesions, perianal papules, and a dry ulceration of the glans penis (relapse).

<sup>3</sup> Lesions of lips, genitals, and perianal region.

\* From Ven. Dis. Inform.

Although the organism cannot be demonstrated by darkfield examination in gummata and other late pathologic manifestations of syphilis, its presence may be revealed by animal inoculation.

**Presence in Body Fluids.** In the early stages of the disease, certain of the body fluids contain treponemata. Under some circumstances these fluids may be of practical importance in the transmission of syphilis. In experimental syphilis in the rabbit, the *T pallidum* may be demonstrated, in some instances, in the blood stream within a matter of hours after inoculation. Whether this is true or not in man has not been established. (It is conceivable that the trauma of intratesticular inoculation may open channels of invasion not available in natural infection.)

Infectivity of the blood stream is of great importance in blood transfusions. Klauder and his collaborators reviewed the thirty-three cases of transfusion syphilis reported in the literature during the two decades following 1915. In most cases the attending physicians were unaware of the presence of the disease in the donor. The longest duration of known syphilitic infection in a donor was seven years. The donors in one-fifth of the cases were apparently incubating the disease at the time of the transfusion since these were seronegative. This constitutes evidence for the belief that the blood stream is invaded early in the disease, certainly before the diagnostic serologic tests become positive. (*T pallidum* apparently disappears from citrated blood in 72-96 hours when stored at 5° C. This is an important fact in the management of blood banks.)

The cerebrospinal system may be invaded early. It has been shown that the *T pallidum* may be demonstrated in the spinal fluid as early as three weeks after infection. Various studies have indicated that the organism was present in from 15 to 26 per cent of early cases, in which the spinal-fluid examination was negative by the usual laboratory studies.

**Presence in Body Excretions.** Proof is wanting that the *T pallidum* is excreted from glandular structures such as sweat glands, mammary glands, and salivary glands. In the absence of active mouth lesions, the saliva has not been found to be infectious. Reported cases of infection in infants suckling the breast of an infected wet-nurse have not excluded the probable presence of active secondary lesions about the breast or nipple.

Because syphilitic infection is acquired in most instances through sexual exposure, the secretions of the genital tracts have been closely scrutinized. Since it has never been shown that glands excrete *T pallidum*, there is no reason to suppose that an exception occurs, let us say, in the testes, seminal vesicles, or prostate. Certainly it is common knowledge that infection usually results from the presence of moist lesions about the genitalia. Thus the demonstration of a certain incidence of infectiousness of semen in early cases can be explained by the presence of infectious mucosal lesions within the urethra, let us say. Kemp, in an analysis of studies reported on investigations of the semen in 144 persons, found that the treponema was demonstrable in one-fifth of the early cases (usually instances of secondary and

relapse syphilis), and that in only one of fifty-two late cases was semen found to be infectious. It thus appears probable that infectiousness of the semen is related to mucosal secondary or relapse lesions in the urogenital tract, rather than to excretion by the glandular structures.

Pariser studied the infectiousness of the vaginal secretions and menstrual blood of syphilitic women. He concluded that the *T pallidum* was discharged only in the presence of local lesions of either early or relapsing syphilis, and that menstrual blood was infectious only in the patient with early syphilis. Other physiologic secretions were not found to be infectious.

#### INFECTION BY THE *T pallidum*

From the foregoing discussion the deductions bearing upon the infectiousness of syphilis are quite clear-cut. The proper understanding by the physician of these epidemiologic factors is essential in the management of the acute stages of the disease, in the matter of contact investigation, and for the intelligent education of the public relative to syphilis as an infectious disease.

Clinical and experimental evidence indicates that *T pallidum* is capable of penetrating the unbroken mucous membrane. The facts that it is an anaerobic organism, and that it promptly succumbs to drying, make the prerequisites for infection clear. An individual, to be infected, must have intimate contact between a moist surface of his body with that of the infectious person. This contact practically always implies either an oral or a genital one. Uncommonly, the organism is transmitted by fomites from the moist lesions of the infectious patient, without time for drying, to the mucous membranes of the contact, as by drinking utensils, chewing gum, rectal or vaginal douche tips, and the like.

It is believed that the unbroken skin, for practical purposes, is impervious to infection. Therefore it is presumed that when the skin is the portal of entry, it is essential that there be a break in it. Infections among dentists, nurses, and physicians most often occur about the fingernails where there often are fissures in the skin. Inoculation of organisms may take place by direct penetration of the skin by surgical instruments or needles contaminated with secretions from lesions or with blood from patients in the infectious stage of the disease.

#### INVASION AND PATHOLOGY

After the *T pallidum* has invaded the host, a pathologic change occurs which is fundamental to the pathology of syphilis irrespective of the tissue. The organism multiplies in the perivascular lymph spaces. There is an accompanying obliterative endarteritis. The perivascular tissues present an infiltration by plasma cells and lymphocytes. Subsequently fibroblastic

activity leads to healing at the syphilitic focus. During the active stage of inflammation the treponemata multiply, invade the lymphatics of the area, and thus reach the regional lymph nodes causing the characteristic lymphadenopathy associated with the primary lesion. From here invasion of the blood stream is rapid, with the localization of the organisms at multiple foci in the body.

## THE ORGANISM AND THE HOST

Syphilis as an infectious disease cannot be fitted into the pattern of the course of bacterial disease as we know it. The probability is that the course of syphilitic infection is related in a greater degree to the individual peculiarities of the host rather than to any theoretic variations in strain or virulence of the invading organism. (We have seen in a family whose several members were infected, each from a different source, a lesser development of a protective mechanism than is usually expected, as measured by a tendency to relapse.) The objectives of this volume are not such as to warrant any extensive discussion of these matters. However, brief references will be made to important factors so that the trend of thought in the field of host resistance or reaction may be sensed.

### HOST FACTORS IN INFECTION

Everyone exposed to syphilis does not acquire the disease. Investigation of contacts reveals that only about one-half of those exposed to a given infectious case actually develop the disease. It is known that certain prostitutes after years of exposure still remain free of the disease. Certainly these are more than matters of chance.

Furthermore, if infection does take place it may be either symptomatic or asymptomatic in its early stages. The explanation of this is difficult. In the experimental animal it has been shown that the number of organisms can be reduced to such a point that, though a given number will always produce an infection, such invariably occurs without the development of a chancre at the site of inoculation. May this occur in natural syphilis in man? Apparently in experimental syphilis attendant bacterial infection causes a more severe syphilitic infection, that is, local infection at the site of inoculation may lead to more extensive chancres. These may be factors in human syphilis as yet unrecognized, but nevertheless partially explanatory of the possibility of an infection being either symptomatic or asymptomatic in the early stages of the disease.

The sex of the patient is an extremely important factor in the course that syphilis is to take. All observers agree that syphilis presents a much more benign course in the female than in the male. A history of acute syphilis is less frequent in females than in males. By many this has been



thought to be due to the fact that the chancre may be in an inaccessible site, and therefore the lower incidence of primary syphilis is more apparent than real. However, the incidence of secondary syphilis is lower in the female than in the male. (That asymptomatic infection may occur is clear to us. We have followed females who had been contacts of men with acute syphilis, from the seronegative to the seropositive stage in which careful weekly examinations of the external genitalia and vagina have revealed no visible lesions at any time.) Some investigators believe that pregnancy reduces the probability of acute manifestations of the disease if it was acquired at such time. Even in late syphilis we know that the course of the disease is more benign in the female. All statistics point to the fact that cardiovascular and central nervous system syphilis are less frequent in females than in males. This variation is greater than can be explained on the difference of the disease prevalence in the two sexes. The female sex hormone may be the basis for this difference. Experimental work has been reported showing that syphilis is more severe in the castrated female rabbit than in controls, also that male rabbits may be given sufficient theelin to reduce the severity of inoculated syphilis to the benignity expected in the female animal.

Age is certainly a factor in the host reaction to the syphilitic infection. The fetus infected in intra uterine life frequently succumbs to the acute infection, whereas the patient with acquired syphilis rarely dies of the disease as an acute infection. Syphilis kills by the late results of long standing tissue change.

Race is a factor which cannot be disregarded with respect to the reaction between host and invader. Surely the clinician treating syphilis in both the white and Negro races is struck by the difference in the morphology of the skin reactions in the secondary stage of syphilis. Furthermore, cardiovascular syphilis is much more common in the coloured than in the white patient, and by contrast it is generally accepted that the reverse is true with respect to the incidence of central nervous-system syphilis.

**Reaction to Treatment** Lastly, there is that inexplicable fact that some patients who have had treatment, adequate or inadequate, begun in the acute stages of the disease may be seen subsequently with relapse or late lesions. By contrast, there are others who after only a few treatments show a reversal of the serologic tests and, when examined fifteen years later, will be without any clinical or serologic evidence of syphilis. Many clinicians can point to numerous such examples.

The explanation of these several important facts has not been forthcoming as yet, but unquestionably they are to be explained on the host parasite interrelationships.

## IMMUNITY

Not only are the several above factors of interest, but the reactions to the disease within the host are very intriguing because of their variability from time to time. This leads to a resume of what little is known of immunity in syphilis.

In the bacterial diseases one may conceive of a "complete immunity" following the elaboration of certain antibodies during the original immunizing attack. In syphilis this concept is not tenable, for it is a disease in which paradoxical reactions occur between invader and host. Thus after the appearance of the primary lesion, successful inoculation of the treponemata at another site in the skin is possible for only a few more days. Subsequent inoculation is impossible. Yet though one may speak of tissue immunity (of the skin in this case), the patient not only develops secondary lesions of the skin, but the chancre and the skin lesions do not prevent the widespread dissemination of the organism throughout the tissues of the body and the development of foci of inflammation which persist and recur over a period of many years. Probably a given tissue may develop a high degree of immunity, and another low. (There is experimental evidence in the rabbit, for example, that the cornea does not take part in the general immunity. Inoculation of *T. pallidum* into this structure in a treated syphilitic rabbit may result in a lesion, whereas inoculation elsewhere will not produce a reaction.) On the other hand, reactions in certain tissues may contribute in some degree to the general immunity. Thus it is commonly accepted that a widespread skin reaction, as may occur in secondary syphilis, will have a favourable effect upon the course of the disease in general.

After the early stages of the disease, the course of syphilis may vary depending upon the immune reactions in the host. In the greater number of patients the disease is manifested by a low-grade inflammation, which upon resolution is replaced by fibrosis. This low grade process maintains a level of immunity which permits the disease to remain latent. This is not necessarily a benign process since the end result of this gradual scarring may be unfortunate. An example would be the changes which may occur in the aorta where dilatation and aneurysm may be the end results of the chronic progression of the proliferative process. In a lesser number of patients the products of the treponemata, either elaborated by it or resulting from its destruction, may so sensitize certain tissues as to render them "allergic" to these products. The subsequent invasion of such sensitized areas by so few organisms that they cannot be demonstrated on section or darkfield examination may result in an explosive reaction with tissue destruction characteristic of the gumma. (The same type of reaction

may occur in early syphilis in the presence of trauma. Apparently abnormal or damaged tissue, as in the case of burns, contusions, incisions, and the like, when invaded by the *T. pallidum* may produce a late type of reaction. This may be seen in early syphilis before sensitization could reasonably have taken place.) The gummatous reaction is startling because so few organisms can produce such a violent destructive reaction, in contrast to the nondestructive reaction in secondary syphilis where skin or tissues may be literally teeming with organisms.

**Reinoculation or Reinfection.** An interesting phase of immunity in syphilis is the question of reinoculation or reinfection. As already mentioned, after the appearance of the chancre, the period of time within which the skin is susceptible to successful reinoculation can be measured only in days. Subsequent to this period the body surfaces will not again respond to the introduction of *T. pallidum*. This has led to much speculation as to the mechanism involved in this refractoriness. One school of investigators feels that reinfection could take place only if every organism were eliminated from the body (biologic cure), thus indicating that skin immunity is dependent upon the persistence of treponemata in the body. The other school does not subscribe to this, but believes that tissue immunity is not dependent upon persistent infection.

A puzzling phase of the problem is the fact that, although in early syphilis the skin is immune to treponemata entering from the outside, it will react to a new spread of the organisms in the body as in the case of relapse. Chesney advances the theory that the treponemata within the host develop resistance against treponemicidal products elaborated by the tissues of the host.

The problem of mucocutaneous relapse and neuro-relapse (invasion of the central nervous system as a relapse phenomenon) is of great practical importance when related to treatment of acute syphilis. Mucocutaneous relapse is a phenomenon of the early years of syphilis, and apparently represents a local decrease of immunity. With multiplication of organisms and their general diffusion in the body, infectious lesions again appear in the mucous membrane or skin. The interrelationship of relapse and treatment should be ever present in the mind of the physician in the treatment of the early stages of syphilis—that is, during the first few years. Thus inadequacy of treatment because of either (1) inadequate dosage of the arsenicals, (2) short courses of arsenicals, (3) prolongation of the first bismuth course, or (4) irregularity of treatment, may result in a tendency to relapse. The explanation is that treatment interferes with the development of the natural tissue immunity of the host. With inadequate treatment, even though the skin is refractory to reinoculation (reinfection), the mucous membrane, skin, and other tissues have insufficient immunity to

withstand a new invasion by a multiplication and diffusion of organisms within the host

**Hypersensitivity.** Another, somewhat different phase of the effect of inadequate therapy on immunity is the production of allergy or hypersensitivity in the host, especially by continued inadequate dosages. Such treatment may destroy sufficient organisms to permit the development of a sensitivity of tissues to the products of the treponemata, but not sufficient to control the infection. Under such circumstances one may see a change from the usual type of relapse manifestation to a lesion approaching in type, or actually representing, a tertiary destructive process

### THE NATURAL COURSE OF THE DISEASE

Following the foregoing discussion of the *T pallidum* and the response evoked in the host as the result of invasion by it, a review of the natural history of syphilis may be of benefit. I have found this can be most clearly summarized with the aid of a diagram used by Morgan. Thus we should think of an active disease process which presents clinical manifestations—those conditions indicated above the “clinical horizon” in the diagram. Again we must think of the disease as smouldering, giving rise to no clinical manifestations—the stage of latency, below the “clinical horizon” (Fig 2)

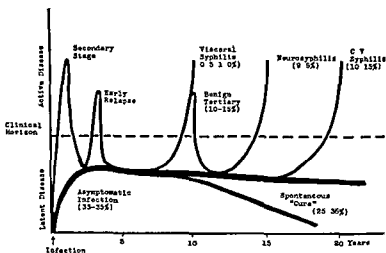


FIG 2 Diagram illustrating the possible natural courses of untreated syphilis (Courtesy of Dr Hugh J Morgan South Med Jour January 1933)

The course of syphilitic disease unmodified by treatment may be briefly summarized with reference to the diagram. Following the entrance of the organism into the body of the host, a generalized infection ensues speedily but does not immediately give rise to any recognized lesion. There is

no question that in a minority of cases the infection always remains latent

With the appearance of the primary lesion the infection has made itself manifest. It may, after spontaneous healing of the chancre, subside to a latent state. More commonly, the symptoms and signs of secondary syphilis appear either following the healing of the chancre or during the latter part of the primary stage. After the spontaneous subsidence of the acute manifestations, the infectious process changes from a generalized infection to the focal infection of latency. During the early years of the disease, however, immunity of the mucous membranes and skin is not complete, and relapse or recurrence may occur. (This is especially true in inadequately treated cases since there has been interference with the development of natural immunity.) Generally, by the time four years have passed in the natural course of the disease, immunity of the mucous membranes and skin has been so firmly established that relapse is practically unheard of, and the infectious stage of the disease is ended.

Latency, the state of scattered focal areas of infection, may then be maintained for decades. The only evidence that occasional showers of *treponemata* appear in the blood stream is provided by the fact that in this latent stage the pregnant woman may infect her child *in utero*. Subsequent to the establishment of latency the host may never again be aware of the infection he is harbouring. In those not so fortunate, the proliferative and destructive lesions will appear later in several years or several decades. Thus the later course may be that of lesions of late benign syphilis or those of slowly progressing cardiovascular or central nervous system changes which may become manifest only after many years.

In certain patients spontaneous "cure" undoubtedly occurs. How frequently this occurs it is impossible to say, for in routine surveys for the prevalence of syphilis such cases are missed. The following case is an example of such "cure."

**Case 1** A coloured female, aged thirty seven years, was seen at Vanderbilt University Hospital in 1927 for complaints unrelated to syphilis. At that time she gave an excellent description of the occurrence of a genital primary lesion and secondary manifestations in her husband, and following this in herself in 1911. Upon admission to the Medical Clinic in 1927, the Wassermann and Kahn tests on the blood were positive on several occasions. No treatment was taken. The patient was again seen in 1938. At this time the blood tests were repeatedly negative. Physical examination, spinal fluid reactions, and teleröntgenograms were all negative.

With this brief summary of what is known or accepted in the present state of our knowledge relative to the biology of the syphilitic infection,

it is hoped that the reader will have greater interest in and understanding of the clinical features of the disease and its treatment to be considered in later chapters

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### III

## THE EXAMINATION OF THE PATIENT

THE material upon which the diagnosis of disease is based is obtained by three methods of procedure the history, the physical examination, and the laboratory studies. A diagnosis of disease is reached only after an evaluation and correlation of the information gathered by these methods of examination.

All too commonly in this day of many and varied aids to diagnosis, the physician neglects the history and physical examination and leans too heavily upon the laboratory for a diagnosis. In certain sections of this book it will be difficult to emphasize the proper perspective in which the three fundamental methods of diagnosis must be viewed. Often I must strongly emphasize that the clinical impression of syphilis (especially syphilis in the infectious stage) must always be verified by laboratory study. On the other hand, great care must be exercised, in the absence of clinical manifestations, that the reports of laboratory tests do not lead one into a diagnosis of syphilis when the disease does not exist. The proper interpretation of doubtful or positive serologic tests at times is one of the most delicate problems the physician must face in the field of syphilis. In this day of premarital blood tests, every physician will be confronted time and again with a doubtful or positive serologic test for his interpretation.

Someone has said, "Syphilis is no longer a disease but a serologic reaction." This ironic statement is all too apt, especially in the diagnosis of latent syphilis. It is therefore essential that consideration be given to the history and physical examination in the management of the syphilitic patient. This is important not only in evaluating positive serologic reactions, but in arriving at decisions as to prognosis, the necessity of treatment, and the kind of treatment, if any, indicated.

## THE HISTORY

Syphilis is an infectious disease, and therefore the history in such an instance should require no special technic over that used in any other disease. From a practical viewpoint I know that the health officer in a clinic handling dozens of patients must reduce history taking to an absolute minimum. Time can often be saved in public-health clinics by the use of a "check-form" of history sheet or card.

## HISTORY OUTLINE

We believe that the following history outline represents the minimum of information that should be obtained and put in writing on the record of any given case

**Complaint**

(The statement given by the patient as his reason for presenting himself to the physician or clinic )

**Present Illness**

(Information which is pertinent to the various stages of syphilis should be obtained if at all possible Obviously the information acquired with respect to these points will vary with the stage of the disease In the primary or secondary stage the patient may give detailed information about the chancre The patient with syphilis of many years' duration, on the other hand, may be able to recall only the approximate date of a possible chancre, the details relative to the lesion having slipped from his memory Yet, as was indicated earlier, the duration of the infection may play an important part in decisions relative to treatment. Therefore, even in the apparently late case, a history of acute syphilis should be obtained if possible )

In past or present disease suggestive of acute syphilis, questioning should bring out the following details to assist in the diagnosis either at the present time or in retrospect

**Primary Lesion**

- 1 Date of appearance
- 2 Time relationship to sexual or other exposures
- 3 Location of the lesion, and its duration
- 4 Characteristics, as pain, tenderness, bleeding, multiplicity
- 5 Regional lymphadenopathy, and its course
- 6 Results of darkfield examination, if done
- 7 Type of treatment used, and its results

**Secondary Lesions**

- 1 Date of appearance
- 2 Time relationship to the appearance and course of a primary lesion
- 3 Site and type of lesions—mucous membrane, skin, or genitalia
- 4 Description of skin rashes, as to kind, distribution, itching, or discomfort.
- 5 Involvement of eyes, joints, alopecia, and lymph nodes
- 6 Systemic symptoms, as fever, anorexia, weight loss, generalized aching, vomiting
- 7 Recurrent secondary lesions
- 8 Headache or other more severe neurologic manifestations
- 9 Type of treatment, and results



In patients in whom syphilis has been of some years' duration, questioning should have as its object the focusing of attention upon structures commonly involved in late stages (As was indicated before, whatever information is available relative to the acute stages should be recorded )

Questioning, in an attempt to bring to light late manifestations of syphilis, should include a search for the following

#### **Late Syphilis.**

- 1 Eyes—*iritis, keratitis, chorioretinitis, optic neuritis*
- 2 Ears—nerve deafness
- 3 Nose, throat, tongue—gummatous ulcers
- 4 Cardiovascular—dyspnea, orthopnea, paroxysmal dyspnea, edema, cardiac pain (The effect of exertion relative to dyspnea or pain )
- 5 Bone—pain and swelling
- 6 Central nervous system—headache, impaired vision or blindness, lightning pains, sphincter and gastric crises, loss of libido, incontinence, paresthesias, gait changes, speech difficulties, personality changes, *memory loss*
- 7 Skin—site and type of lesions, their duration, with effect of treatment

In recent years more and more persons, either by compulsion or voluntarily, have been having serologic tests for syphilis made and therefore valuable information may be forthcoming if the following points are covered

#### **Serologic History.**

- 1 Previous blood tests with date, person by whom blood was drawn, serodiagnostic laboratory where blood was examined, if possible
- 2 Results of test, and advice given
- 3 Results of spinal fluid examination

Often in the evaluation of doubtful blood tests or even positive tests in a person who denies any knowledge of syphilitic infection, the following details may offer important collateral information

#### **Marital History.**

- 1 History of infection in the partner, as to duration, type of lesions, and treatment
- 2 Results of blood tests in spouse.

#### **Pregnancy History.**

- 1 List pregnancies and their outcome as to miscarriages, still births, syphilitic and healthy offspring
- 2 Treatment during pregnancies

**Family History.** (Pertinent in patients with congenital or possible congenital syphilis )

### History of Treatment

- 1 Time, regularity, number of various types of injections
- 2 Site of injection, colour of drug, taste, etc
- 3 Treatment given by whom
- 4 Treatment reactions

At times further details may be of interest. In latent cases in which no history of acute syphilis is obtained, one may at times obtain clues as to the possible duration of syphilis by inquiry with regard to the patient's sex life, e g age at which sexual exposure began, attacks of one or other of the genito-infectious diseases such as gonorrhea, chancroid, lymphopathia venereum, or granuloma inguinale.

For the student and the inexperienced historian, it is probably not out of place to point out the need for the use of colloquial terms in history taking. In the clinic it is not unusual to obtain a history of a primary lesion after the student obtained a negative answer to a query regarding "chancre." The terms used among the uneducated to designate syphilis vary with sections of the country, but may be "syph," "bad blood," "the pox," "hair-cut," "hard chancre," or merely "a sore."

Furthermore, in taking the history of a patient with acute syphilis, he or she may categorically deny sexual intercourse. The student or physician is too prone to consider the patient a liar. As a matter of fact, it is not unusual to meet with the belief that actual coitus is necessary for transmission of the disease. Patients may deny sexual intercourse, but freely admit other intimacies and sex play and express surprise that disease may be transmitted in this way. Case 16 presented this problem. Upon taking her history relative to contacts, she firmly denied sexual exposure. In answer to a question of "Did you almost have sex relations?" she freely admitted sex play with another roomer in her boarding house, but asked, "Can you get it that way?" Case 2 illustrates further that the patient may be truthful in denying sexual intercourse as the term is usually used.

**Case 2** An eighteen year-old white college girl was referred for examination because of a genital lesion of three weeks' duration.

She persistently denied sexual intercourse and sex play. Finally she admitted cunnilingus on the part of her fiance. They had indulged in this intimacy in the past. Then it was interrupted for a prolonged period of time due to the patient's hospitalization for a surgical condition. (At the time she was in the hospital she was found to be seronegative.) After her discharge from the hospital, the patient admitted that these intimate relations had occurred on two occasions, following which she took a vacation trip. Two weeks after the last exposure to her fiance she became aware of the genital lesion.

Examination was negative for that of the vulva. The vaginal orifice was virginal. On the medial surface of the left labium majus, at the level of the

clitoris, was an infiltrated round tumefaction 1 cm in diameter. This was not tender and felt like a button under the epithelium, the surface was slightly denuded but clean. The left inguinal node was enlarged and tender.

Darkfield examination of serum obtained from the lesion contained *T pallidum*. The blood Wassermann test was negative, the Kahn test positive.

**Comment** This case illustrates the fact that the patient may be honest in a denial of sexual intercourse, and a lay person may well be unaware that such oral contact might transmit syphilis. This patient probably really believed that she contracted the infection from a toilet seat on the train. She raised the question of this possibility. It shows the need for further questioning in contact investigation if the usual forms of exposure are denied. Very probably this girl's fiancé acquired syphilis during her ten week period of hospitalization and subsequently infected her through mucous patches in his mouth.

Lastly, one must realize that homosexual patients may truthfully deny heterosexual contacts.

Finally, in history taking, one must be prepared to accept innocently acquired infections as a probability. Proved cases of syphilis acquired innocently in childhood, youth, and adult life are not uncommon in the experience of any clinician treating much of this disease. Therefore, there must be numerous cases of innocent infection among patients with latent syphilis, who deny acute infection and sexual exposure. One wonders how often a primary lesion in youth, or even in adult life, is either unrecognized or passed over as a sore of only passing interest.

## THE PHYSICAL EXAMINATION

Though the physical examination should always be complete, the emphasis on certain phases of the examination will vary with the stage of the disease. One does not expect to find an aortic aneurysm in a patient with secondary syphilis, nor does one expect to find perianal condylomata in a patient suffering from general paresis. This does not mean, however, that any part of the examination should be slighted, since nonsyphilitic chronic disease of one system or another may play an important part in the decision as to the safety of antisyphilitic treatment or to the type of treatment to be used.

### OUTLINE

The physical examination should include reference to the following items:

**Temperature**—for the presence of fever, which may occur in acute, or at times in some forms of late, syphilis.

**Skin**—if a rash be present, details as to distribution, colour, size, and an accurate description as to the type of lesion: macular, papular, etc.

**Lymph Nodes**—whether involvement is localized or generalized, characteristics of the enlargement relative to size, tenderness, fluctuation, skin over the nodes, etc

**Hair**—alopecia

**Ears**—nerve deafness

**Eyes**

**FUNDI**—evidence of chorioretinitis, optic neuritis, optic atrophy

**PUPILS**—equality, regularity, pupillary reflexes

**IRIS**—iritis, adhesions from former iritis

**CORNEA**—keratitis, or evidence of former keratitis as shown by scars or vascularization

**Nose**—discharge, crusts, perforated nasal septum, saddle nose

**Mouth**

**MUCOUS MEMBRANE**—mucous patches, gummatous infiltrations, deforming scars of former gummatous pharyngitis, rarely, chancre

**TONSILS**—mucous patches, gummatous lesions, rarely, chancre

**TEETH**—stigmata of congenital syphilis

**Neck**—goiter, venous distention (symmetrical in cardiac disease, asymmetrical in mediastinal disease, as in aortic aneurysm), pulsation, tracheal tug, tracheal deviation

**Heart**—size, determined by inspection, palpation, and percussion, abnormal pulsations of the chest wall, and suprasternal pulsation, bulging of the chest wall, on auscultation, murmurs or bruits, retromanubrial widening of percussion dullness, thrills, blood pressure bilaterally for variations, pulses with respect to asynchronicity, differences in volume, "Corrigan" and capillary pulse

**Chest**—inspection, palpation, and percussion relative to pulmonary disease, auscultatory evidence of bronchial obstruction and moisture

**Abdomen**—masses, palpability of viscera

**Genitalia**—lesions location, appearance, tenderness, number, moisture or dryness, urethral discharge, scrotum skin lesions, abnormalities of its contents, vaginal examination

**Rectal**—anal condylomata, moist erosions, prostatic abnormalities, etc

**Extremities**—edema, abnormalities of bones, arthritis, periostitis

**Nervous System**—in addition to fundi oculi and pupillary reflexes, abnormalities of the cranial nerves, in the extremities tremors, gait, ataxia, tests of vibratory sense, deep and superficial reflexes, motor strength, Romberg test, sensory changes

**Mental**—memory changes, behaviour, test phrases

## LABORATORY STUDY

Routine laboratory study should include urinalysis. It is essential to know whether or not nephritis or diabetes mellitus is present. Examination of the blood for the presence or absence of anaemia is important. At times

the blood smear is of great importance, especially in the differential diagnosis of other diseases from possible latent syphilis suggested by positive serologic tests. The demonstration of the malarial organism or unusual blood cells in a smear may be essential in diagnosis.

### THE DARKFIELD EXAMINATION

Only a brief note concerning this method of examination will be made, because darkfield examination, and especially the recognition of the *T pallidum*, cannot be learned from a book. The need to differentiate the *Treponema* from nonpathogenic spirochetes of the genitalia or mouth, especially in the case of the latter, requires that the darkfield diagnosis of syphilis be not undertaken lightly.

Briefly, the principle of darkfield illumination is as follows. By means of a special substage condenser, the light rays reflected from the centre of the mirror are not permitted to pass through the condenser. The rays from the sides of the mirror are bent at a 45° angle. Thus only those rays striking a translucent object in the microscopic field are refracted up to the eye. The object thus appears as a "bright" object in a black field.

Slides and cover-slips used must be clean and free of scratches. Serum expressed from lesions should have, upon darkfield examination, a scattering of several red blood cells per field, thus indicating that material has been obtained from some depth.

In obtaining material for darkfield examination from chancres, condylomata, or moist erosions about the genitalia, the following procedures may be used. The lesion is firmly grasped at the base by the gloved fingers, so that a relative ischemia is produced. The lesion is cleaned with a saline sponge. In lesions which are of relatively short duration and moist, sufficient serum may be obtained by merely abrading the surface with dry gauze. Slight bleeding may occur. The blood is wiped off until clear serum exudes. In the case of drier, old, or involuting lesions it may be necessary to scrape the surface of the lesion with a dull scalpel until a slight oozing of blood occurs.

One practical point to keep in mind in examination, especially of genital lesions of either primary or secondary type, is the possibility of previous local treatment. Frequently, as the result of consultation with a druggist or friend, the patient applies one of the many drugs used for local treatments. These range from calomel ointment through potassium permanganate, copper sulphate in solution or crystals, phenol or lysol, mercury bichloride, iodine, etc. We have seen the use of glycerine tampons in the vagina associated with enough leakage of glycerine to destroy the superficial organisms in condylomata. All of these chemical agents may destroy the superficial organisms to such an extent that darkfield examination may

be unsatisfactory for the next eight to twelve hours. In the event of negative examinations following local treatment with chemicals, the application at intervals of hot saline packs to penile lesions, or of hot sitz baths in females, should be advised. Re-examination the next day may be rewarded with a positive result upon darkfield study.

In obtaining serum from mucous patches on the lips, the same methods are used as just described. I find a small, dull curette a practicable instrument for the collection of material for darkfield examination from mucous patches on tonsils or soft palate. The curette may also be used to obtain scrapings from the cervix of the uterus. Darkfield examination of serum or scrapings obtained from dry skin lesions does not yield as many positive results in as high an incidence as in the case of moist lesions. Hence the method to be followed is to cleanse the skin over the papule, let us say, with alcohol. The epidermis is then scraped with a dull scalpel until a small amount of serum exudes. This is used for examination. If no serum can be obtained, a small drop of normal saline may be placed on the slide or cover-slip, and scrapings from the skin lesion may then be mixed with the saline.

If no lesions are available for examination, aspiration of a lymph node may reveal *T. pallidum*, especially in the case of the sentinel node. The skin over the node is prepared with iodine and alcohol. A small syringe with a tightly fitting plunger fitted with a 20-gauge needle and containing 0.1 cc. of normal saline is used for aspiration. The fingers of one hand fix the node. The needle is directed into the node, the saline injected, and the tip of the needle is then moved about within a small arc to break up the tissue. Material is then aspirated, only enough may be obtained partially to fill the needle. This is forced out upon a slide, a cover slip is firmly pressed down to form a thin film, and darkfield study made.

There may be phimosis due to edema of the prepuce, with a chancre on the glans or on the inner aspect of the prepuce. At times we have been successful in demonstrating the *Treponema* in saline washings from under the prepuce in such cases. First the area is irrigated with normal saline solution by means of a pipette fitted with a rubber bulb. Then more solution is instilled and aspirated for study.

Some state health departments provide for the darkfield examination of material collected in capillary tubes, which are sent by mail to a central laboratory. We have demonstrated actively motile treponemata in serum from condylomata or chancres, collected in capillary tubes and sealed with wax, after they have stood at room temperature for seventy-two hours. However, a negative examination in such specimens does not prove that the lesion in question is not syphilitic.

STAINING METHODS FOR *T pallidum*

At intervals new methods are announced for staining the organism of syphilis. For the purpose of this book, I shall dismiss the subject by the comment that no method to date is of practical value in the accurate diagnosis of syphilis.

## VENIPUNCTURE

Drawing specimens of blood for serologic tests for syphilis requires no discussion. Every physician interested in the treatment of syphilis presumably is capable of venipuncture. At least 5 cc of blood should be collected so that sufficient serum will be available for examination in the laboratory.

## SPINAL PUNCTURE

Spinal fluid may be obtained by either cisternal or lumbar puncture. A description of the simple technic involved in obtaining spinal fluid will not be given. If the reader is not familiar with the technic, the best way to learn it is to have assistance for a few times in the performance of the operation. It is best to collect spinal fluid in two tubes. For the globulin test and cell count 1 cc will be sufficient in one tube. In the other, 4-5 cc of fluid should be collected for the Wassermann test and colloidal test.

## MISCELLANEOUS PROCEDURES

Blood counts, the icterus index, liver- and kidney-function tests, all may be necessary in certain phases of syphilis or its treatment. The indications for these will be discussed in their proper places relative to diagnosis, prognosis, or therapeutic complications. So too, the electrocardiogram and the roentgen ray examination must be used at times for assistance in the diagnostic problems taken up in subsequent chapters.

In summary, it cannot be too strongly emphasized that the proper diagnosis and management of the syphilitic patient is impossible without an adequate history, physical examination, indicated laboratory studies, and their proper evaluation.

## IV

# THE SEROLOGIC DIAGNOSIS OF SYPHILIS

## HISTORICAL NOTE

THE complement fixation test for syphilis was described by Wassermann, Neisser, and Bruck in 1906. This was based on the Bordet Gengou complement fixation phenomenon. Wassermann used fetal syphilitic liver as an antigen with the idea, later proved false, that the treponemata in the liver provided the antigenic substance. Subsequently it was shown that extracts of normal organs may be used as the antigen in the test. The one commonly used is made from dried beef heart.

The flocculation test for syphilis was first described by Michaelis in 1907. He also used syphilitic liver as antigen. It was not until 1917 that the flocculation test was again suggested for use. At that time Meinicke, by using a beef heart antigen, introduced a new flocculation test. Since then several tests based on this phenomenon have been described. The most common of those used in this country are the Eagle, Hinton, Kahn, and Kline tests, named after their respective originators.

Various modifications of the Wassermann test have been in vogue from time to time. At present, the one generally accepted to be best in the U S A is Kolmer's modification involving the ice box incubation technic.

## TECHNIC OF TESTS

Space will not be given to a description of the technic of performing complement fixation or flocculation tests. Such technics are described in any good textbook on laboratory procedures or in publications of the United States Public Health Service. The skeleton outline of what is involved in the test will indicate the steps involved in the tests and the substances used.

### COMPLEMENT-FIXATION TEST

The complement fixation test rests on the Ehrlich sidechain theory. This is based upon the presence of a thermostabile amboceptor and the thermolabile complement in the blood and tissue fluids of immune animals. These unite with the antigen (a bacterium in the original concept) to destroy the organism. The three substances—antigen, amboceptor, and complement—are necessary to complete the reaction. This system can be applied as well to red blood cells to cause hemolysis. Since complement is the same for the bacterial and the hemolytic systems, a combination of these systems may be used to demonstrate the fixation of complement, the



hemolytic system acting as an indicator Diagrammatically the test may be described as follows

"Syphilitic" antigen (Beef heart extract)	amboceptor + (Heat treated patient's serum)	Complement + (Guinea pig serum)	Syphilitic =serum system
Antigen (Sheep cells)	amboceptor + (Heat treated serum from rabbits sensi- tized to sheep cells)	+ Complement (as above)	=Hemolytic system

Both patient and rabbit sera must be heat treated to destroy complement. The test is so done that an opportunity is given for the upper, or syphilitic serum, system to be completed, i.e. if the patient's serum is that of a syphilitic, complement will unite the amboceptor to the antigen and thus "fix" the complement. (This amboceptor in the syphilitic serum is commonly called reagin.) If then the second, or hemolytic, system is added (without complement, of course), the complement having been fixed, the amboceptor (rabbit serum) cannot unite with the sheep cells to cause hemolysis, the red cells are preserved, and the test is thus positive. On the other hand, if the serum is that of a nonsyphilitic patient, the complement does unite with the amboceptor (rabbit serum), and the antigen (sheep cells) in the hemolytic system, and the red cells will be destroyed or hemolyzed, and thus the test is negative. It may thus be seen that the hemolytic system is merely added to produce a colour reaction to act as an indicator. The hemolysis is expressed as strongly positive, positive, doubtful, or negative, or in the older method of 4-plus, 3 plus, 2-plus, 1-plus, or negative. About twenty-four hours is required to complete the complement-fixation test.

As part of every complement-fixation test, a control tube must be set up without the use of antigen. This must be done, for sometimes the patient's serum may have an effect on complement similar to the union of complement to antigen by amboceptor (reagin). Should this occur, no hemolysis will take place—this constitutes an anticomplementary reaction. It may be due to the use of glassware not chemically clean, to drugs, or to chemicals in the blood (at times arsphenamines in the blood) and to sera which are not fresh and are contaminated with bacterial growth. Anticomplementary reactions may occur at times in nonsyphilitic disease which cause biologic false-positive flocculation tests.

#### FLOCCULATION TESTS

The flocculation or precipitation tests, in contrast to the time-consuming and much more complicated complement-fixation test, are simpler and done

more rapidly. The various flocculation tests differ essentially in the preparation of the antigen from beef heart. The test consists of mixing an antigen solution with some heat-treated (inactivated) patient serum. If the serum is from a patient with syphilis, a precipitate forms in the mixture. The degree of positivity is estimated by the use of several tubes with varying amounts of antigen. Flocculation tests can be completed in one hour.

Both the complement-fixation and the flocculation tests can be made the basis of quantitative determinations by the use of varying dilutions of patient's serum. The reader may find reference to these in the literature, but since such quantitative methods are not applied in laboratories to which the readers of this book will probably turn for their serodiagnosis, further discussion of this type of test is superfluous.

#### TECHNICAL ERRORS

It is essential to realize that technical errors in the performance and reporting of tests for syphilis may lead the physician astray. These include improperly cleaned glassware, errors in the preparation of antigen, and errors in reading the results of the tests. *No technician, no matter how experienced, is superhuman, and no laboratory, no matter how good, is infallible.* To this should be added errors in reporting. Identifying slips of paper may become mixed up, numbering of tubes may be in error, tubes may be misplaced, results may be entered upon the wrong slips or papers. *These facts make it imperative that the diagnosis of syphilis should never be made, in the absence of clinical or collateral evidence, on the basis of a positive report on one blood sample.* With no other evidence, a second sample must be found to be positive before a serodiagnosis of syphilis can be made.

#### MISLEADING RESULTS

##### BIOLOGIC FALSE-POSITIVE TESTS

If it will be remembered that the serodiagnostic tests for syphilis are really nonspecific (that is, that no actual syphilitic antigen is used), it will appear surprising that the test is as specific as it is. Apparently the amboceptor (reagin) which ties complement to the lipoids of the antigen (beef heart) is present in such quantity in a few human beings who are not syphilitic as to give positive tests. Precipitation tests on the sera of lower warm-blooded animals and fowls are commonly positive. Kahn has shown recently that these false-positive or biologic reactions of lower animals and occasionally of man can be revealed in their true nature by doing the test at different temperatures. The biologic reaction in the lower animals, in occasional human beings, and in certain pathologic nonsyphilitic con-

ditions, is more marked at 1° C than at 37° C, whereas the positive sera of syphilitics show more marked precipitation at 37° C than at 1° C

Positive blood tests for syphilis in patients not suffering from the disease offer the practitioner many a problem, and are a source of extreme annoyance. There is no questioning the fact that the serologic tests for syphilis constitute our greatest "all-round" diagnostic aid. In large numbers, that is, in the broad aspects, they offer an accurate diagnostic method with an error that is negligible. This does not alter the fact, however, that, in the individual case, many doubts may be raised by a positive test for syphilis. This is especially true in the groups of the population in which the prevalence of syphilis is admittedly low. The problem has been brought home more acutely to the practitioner in recent years because of the passage of premarital examination laws by the various states. (In some of these, incidentally, little allowance is made for individual interpretation.) It is the rare physician in these days who does not have the burden of interpretation of positive serologic tests for syphilis among his private patients. Therefore it is necessary for him to know under what circumstances the serologic tests may present biologic false reactions. (These reactions represent positive tests under circumstances in which no technical error enters into the picture.) Biologic false tests for syphilis may occur as the result of some other disease, or may represent some as yet unknown individual biologic idiosyncrasy.

In the early days of the Wassermann test, it was felt that numerous disease states could produce false reactions. Later, with higher specificity, the tests assumed a greater reliability in the eyes of the medical profession. In recent years, under the stimulus of the United States Public Health Service, evaluation studies of such blood tests have been made. These have led to a general re-evaluation of the tests not only from technical viewpoints but also as to the effects of certain diseases. The latter is important. The official evaluation studies relative to specificity employ the bloods of normal individuals on the one hand and of syphilitic patients on the other. No attention is paid to persons having disease other than syphilis.

**Diseases Causing Biologic False-Positive Tests** Certain of the diseases capable of causing biologic false-positive tests are of little interest to us in this consideration.

**TROPICAL DISEASES** Yaws (frambesia), a tropical disease, commonly has associated with it positive complement-fixation and flocculation tests of syphilis. This is likewise true of pinta, another disease of the tropics. Kala-azar also presents a certain percentage of cases with positive flocculation tests and positive, doubtful, or anticomplementary Wassermann tests.

**LEPROSY**, in general, is of little more interest to the physician in this country than the diseases mentioned in the preceding paragraph, although

an isolated instance might be encountered by any practising physician. Under some circumstances syphilis may be suspected with no thought of leprosy, and thus the positive blood test so frequent in leprosy might seem to confirm an erroneous clinical diagnosis. Hazen and his collaborators showed that complement-fixation tests in lepers were positive in 53 per cent and that flocculation tests were positive in 62.4 per cent.

**TUBERCULOSIS** in the past has been thought to give rise to false-positive tests for syphilis. Recently this subject was re-examined by Parran and Emerson. In this study, more than 400 tuberculous patients contributed blood samples. No false-positive reactions occurred with either the Kolmer modification of the Wassermann test or with the Kahn standard test. "Presumptive" flocculation tests gave some false-positive reactions, as did the Hinton flocculation test. The authors point out that those tests giving false-positive results were sensitive tests. Furthermore, they emphasize that these tests were made by the originators of the test, and that hence errors were probably reduced to a minimum. They imply that more errors are to be expected if these tests are done by less accurate laboratory personnel. From a practical viewpoint, however, it appears that tuberculosis is not a disease to cause confusion in this respect.

**MALARIA** As in the case of tuberculosis, much discussion has occurred in the past relative to possible false positive reactions for syphilis in the presence of malaria. Some authors have found no false reactions in the presence of such infection, others have found false-positive tests in from 10-20 per cent of cases. A recent study by Kitchen and collaborators may explain this discrepancy in past studies. These authors had occasion to inoculate twenty-nine patients suffering from nonsyphilitic psychoses with the parasites of tertian and estivo-autumnal malaria. In twenty-five of these patients, careful serologic studies were made before and after clinical malaria developed. All were seronegative before and after the malarial course. All patients who developed malaria showed positive blood tests for syphilis at some time or other during its course. Two had no positive complement-fixation tests, and two no positive Kahn tests. In some instances positive tests were obtained before the febrile period occurred. The "seropositive" period extended as long as four weeks in 48 per cent of cases. During this period of fluctuation, 320 positive and 307 negative tests were obtained. The fact that the blood of malaria patients is not consistently positive is of great importance. This may account for the previous findings reported in the literature. The apparent discrepancies may be dependent upon the time blood was drawn for examination.

In the evaluation studies of 1938, to be mentioned below, various tests were used in a study of bloods from 266 presumably nonsyphilitic persons who had malaria. Positive reactions were obtained in from 4.4-16.2 per

spirochetal disease, and may be associated with transiently falsely positive complement-fixation and flocculation reactions

COMMON CONTAGIOUS DISEASES have been found at times to have false-positive serologic tests for syphilis, especially the flocculation tests, associated with them temporarily. Thus measles, chickenpox, and mumps have been reported to produce such reactions at times. The febrile diseases in children are likely to be accompanied by false tests.

**SMALLPOX VACCINATION** Lynch and her collaborators have demonstrated that false-doubtful or -positive serologic reactions may accompany successful smallpox vaccination. As is to be expected, the more sensitive flocculation tests gave a higher number of false-positive results than did the complement-fixation tests. Falsely doubtful or -positive tests occurred in 43 (16 per cent) of 263 cases of vaccinia. Such reactions apparently may persist for several months after vaccination. The practical aspects of the recognition of such biologic false tests appear in the discussion of Lynch's paper, where such an instance is reported in an applicant for marriage certification.

**OTHER CONDITIONS** At one time or another false-positive serologic tests for syphilis have been ascribed to jaundice, malignant growths, and pregnancy. More careful evaluation studies in recent years have produced no evidence to support these older findings. The incidence of false-positive tests is no greater in the presence of these conditions than in normal persons. Nor is there any good evidence to support the belief that alcohol or ether anaesthesia cause false reactions of any type.

**False-Positive Tests in Normal Individuals.** In addition to the biologic false-positive tests due to nonsyphilitic disease, there are a small number of normal individuals who will be found to have positive tests, especially positive flocculation tests. These probably do not exceed 0.5 per cent of subjects tested.

The more sensitive the tests are made, the greater will be the number of such false-positive reactions. Increased sensitivity in tests to detect syphilis is attained only at some loss of specificity. If it is recalled that the lower warm-blooded animals almost universally show positive reactions, is it not surprising that more human beings do not show false-positive tests! It is in this group of individuals that Kahn's studies of the effect of temperature on the flocculation reactions may establish the fact that they do represent biologic false positivity. Kahn expresses himself as follows relative to false-positive tests in normal persons: "Indeed, it may be said that the difference between the serum of syphilitic and nonsyphilitic persons is quantitative rather than qualitative—that serum of the former type contains a relative excess of an antibody which is generally found in traces in nonsyphilitic serum." He cites experiments in his laboratory

substantiating this statement. Under certain physiologic conditions the amount of this antibody may vary. For a period of time, O'Leary studied a group of nonsyphilitic young women who showed positive precipitation reactions during the menstrual period and negative tests between periods. Senear has had a similar experience. However, other syphilologists, in a study of a large group of women during and between menstrual periods, found no such instances.

**Provocative Test.** At this point, brief consideration may be given to the subject of the provocative test. It has been accepted by many clinicians that in the presence of quiescent or latent syphilis, an injection of arsenic will cause a reactivation at some syphilitic focus which will be reflected by an increased titer of reagin in the blood and a positive blood test. The provocative test has been used by some physicians on patients with doubtful reactions in the hope of bringing out a definitely positive reaction and thus establishing the serologic diagnosis of syphilis. Naturally it has also been used in patients in whom syphilis was suspected but in whom the blood tests were negative. In all fairness it must be stated that doubt was cast upon the provocative test as far back as two decades ago. The provocative test has never given me assistance, in that it has never clarified any diagnostic problem in which aid was sought by its use. Only rarely can the results be expected to be so clear-cut as to warrant an unquestionable serologic diagnosis of syphilis.

Some experimental work by Barnett and his collaborators is of interest here because in a way it confirms the statement previously quoted from Kahn. These authors had published a method to determine the amount of reagin in the blood of persons giving negative serologic tests for syphilis. They showed a quantitative difference between nonsyphilitic and syphilitic subjects, and expressed the amount of reagin in units. In the study of the provocative effect of an injection of arsenic the following was found: the serum of each of thirty-two nonsyphilitic persons contained no more than one unit of reagin before the injection of 0.45 Gm. of neoarsphenamine. Within twenty-four hours of the injection, the reagin had risen to two or more units in all but five patients, and there had been some increase in four of these. In the fifth, no increase occurred until ninety-six hours, when it reached three units. The sera of thirty syphilitic patients were studied similarly. All had had early syphilis, had completed treatment at least a year before, and were seronegative. By their method, Barnett *et al* found the reagin titers to be higher than in the nonsyphilitic patients in three, the mean being 3.2 units. After injection of neoarsphenamine these patients showed a higher reagin content, but the mean increase was 1.3 units as against 1.6 units for the nonsyphilitic group. Nine of the thirty showed no change by forty-eight hours. It seems that such a demon-

tion of reagin in the blood of normal persons, and the effect of neoarsphenamine upon it, makes the interpretation of so-called provocative tests very questionable at best

#### FALSE-NEGATIVE TESTS

Under certain circumstances the blood tests for syphilis may be negative in the face of known syphilitic disease. The fact that the tests are negative in some stages may be well understood

In very early syphilis the reason for seronegativity is obvious. In the stage of incubation, syphilitic reagin may not have been produced as yet. In the seronegative primary stage, the negative serologic reaction is usually explained as being due to such low reagin content that the diagnostic tests cannot detect it, or that no antibodies have been developed as yet. However, Kahn believes that the negative serologic tests mean that there is enough spirochetal antigen in the blood to remove the antibody, and that when the blood becomes positive in the chancre stage, it signifies an increase of antibody over spirochetal antigen.

The rare case of malignant syphilis may present such overwhelming infection that antibody production is suppressed. Such cases are so rare as to be of no practical importance.

In late syphilis the serologic tests may be negative because the foci of inflammatory activity are so circumscribed that they do not stimulate antibody reagin formation in quantities sufficient to be detected by the ordinary diagnostic tests. Such instances occur not only in late latency but also in the active processes of late syphilis. In succeeding chapters it will be pointed out that possibly 5-10 per cent of active late benign lesions may be associated with negative blood tests. Furthermore, about one-third of the victims of *tabes dorsalis*, and about one-fifth of the patients with aortic disease, show negative tests.

During antisyphilitic treatment the activity of the *treponemata* may be so inhibited that the stimulus to reagin formation is reduced to subthreshold levels. This is well illustrated by the appearance of negative serologic reactions for syphilis within a few weeks of treatment in early syphilis, and the so-called serologic relapse after a lapse of treatment over varying periods of time.

#### DOUBTFUL TESTS

In those suspected of having syphilis, doubtful tests may be bothersome. In the laboratory, reports of doubtful reactions may represent technical errors. Such reporting may be used in borderline cases in which the technician is fearful of committing himself and seeks to protect himself by taking refuge in such a report. On the other hand, as the evaluation-study

summary below will show, doubtful tests on blood samples from syphilitic patients may indicate a weak or insensitive antigen.

It is the report of a doubtful reaction in a presumably nonsyphilitic person that is the thorn in the practitioner's side. Under such circumstances the physician's clinical judgment and experience must be called upon for a proper evaluation of the patient's status. One wonders how many unfortunates annually are started on the road of antisyphilitic treatment merely on a report of a doubtful blood test. How many physicians consider this to represent a "touch of syphilis"!

## FLUCTUATION OF SEROLOGIC REACTIONS

It is common experience in the clinic, where frequent tests are done in the same cases, that fluctuations in the reactions are frequent. These may even be noted from day to day. Several factors may operate to cause fluctuating serologic reactions.

I believe it is quite obvious that the blood of all patients need not show the same degree of positivity. If a quantitative evaluation be made on positively reacting blood samples from two different individuals, the titer may be so low in one as to be but slightly above a threshold value for a positive test, whereas in the other the reagin content may be a hundredfold greater. Hence, a slight fluctuation in titer may make one blood subthreshold on occasion, while another remains positive.

The reagin content will surely vary from time to time with the activity in syphilitic foci. An intensified inflammatory reaction at a given site may stimulate antibody production to above threshold values, and later quiescence may be marked by a drop in reacting substance. Obviously this may be influenced by treatment. Fluctuating blood tests may be disturbing to the clinician. Still more paradoxical to the therapist may be the persistently positive serologic reaction during treatment, and its reversal to negative some months after the cessation of treatment.

The fact that reactions for syphilis may be doubtful, negative, or positive on successive tests has been commonly accepted to mean a fluctuation of titer from subthreshold to threshold values. An illuminating study by Mohr and Smith is of practical interest. Bloods were examined quantitatively on the day they were drawn. A portion of the blood was frozen at  $-13^{\circ}\text{F}$ . At a later date, after a number of blood samples from each patient had been accumulated, the frozen sera were examined by the same test on the same day. The accumulated frozen samples tested simultaneously showed little variation, whereas the examinations carried out on the same samples on the day when collected revealed wide fluctuations. These authors concluded that the variations in repeated blood tests in the same syphilitic patient are not due to variations in the reagin content of the



serum, but primarily reflect daily fluctuations in the sensitivity of the tests employed in the laboratory

At this point I cannot resist the temptation to make the following comment upon the relationship of the serologic tests for syphilis to the diagnosis of the disease, and its treatment. The physician should give thought to falsely positive and negative reactions on the one hand, and to fluctuating results of tests in a given patient on the other. *How fallacious is an attitude of staking all in the diagnosis and the evaluation of treatment in syphilis, on the single report from the laboratory, no matter how excellent its reputation!*

## EVALUATION STUDIES

Since the serologic tests for syphilis are admittedly of exceeding importance as aids in the diagnosis of the disease, and because of the inordinate weight given to laboratory reports by all too many physicians, it seemed desirable to make an evaluation of laboratories and the tests used by them. These comparative evaluation studies were made under the direction of the United States Public Health Service.

The comparative evaluation was made by supplying like samples of blood to the laboratories of the originators of the various tests. The tests were thus done under the best conceivable conditions, namely, under the direct supervision of the originators of the tests.

Subsequent evaluation studies included the performance of the various tests not only in the laboratories of the originators, but also in the laboratories of state, municipal, and private agencies. Five such evaluation studies were carried out between 1934 and 1939. These were published in *Venereal Disease Information*, a summary of the studies also appears in Supplement No. 14 to *Venereal Disease Information*.

It does not seem necessary to summarize all of this material, hence a summary of the last study only will be given. The reasons for giving these are several. The reader will not be able to send blood samples from his patients to the laboratories of the originators of the tests. He will have to depend upon his state, city, or nearby private laboratory. He therefore should be interested in what help he may obtain from such laboratories, and how accurate such reports will be as an aid in determining whether or not his patient has syphilis.

## RESULTS

In the 1939 study, blood from 222 known syphilitic patients and from 115 normal, presumably nonsyphilitic subjects were used. These were sent to the control laboratories (those of the originators of the several tests), to 38 state laboratories, and to three Public Health Service laboratories. These laboratories used a total of 31 complement fixation tests and 66

flocculation tests. The results of this study were much better than in the previous studies, for the former had shown the importance of strict adherence to the technic of a test as described by its originator. Lack of this had led to the exceedingly poor showing by some state laboratories in the past. In the 1939 survey 31 of the 43 laboratories followed standard technics. Most laboratories did so in the case of flocculation tests.

**Sensitivity.** The results of the control laboratories for sensitivity (percentage of true-positive reactions in bloods from known syphilitic donors) are shown in Table II.

TABLE II

SENSITIVITY OF TESTS DONE IN THE LABORATORIES OF THE ORIGINATORS OF TESTS. PERCENTAGE OF TRUE-POSITIVE REACTIONS ON SYPHILITIC BLOODS<sup>1</sup>

<i>Test</i>	<i>Per Cent</i>
Kline exclusion	91.0 ( 2 doubtful)
Kahn presumptive	87.6 ( 1     "     )
Hinton	85.5 ( 6     "     )
Kolmer (complement fixation)	83.4 (no     "     )
Eagle microflocculation	82.4 ( 7     "     )
Eagle macroflocculation	80.2 ( 5     "     )
Kline diagnostic	78.8 (20     "     )
Kahn standard	77.4 (18     "     )
Eagle complement-fixation	73.9 ( 8     "     )

<sup>1</sup> From Ven. Dis. Inform., Supplement 14.

**In specificity** (percentage of negative reactions on bloods from presumably nonsyphilitic persons), all but two of the control serologists reported 100 per cent negative tests. Incidentally, the control serologists reported only four false-positives in four years. This sets a goal for other laboratories to achieve.

The laboratories participating in the evaluation studies were rated as satisfactory by the committee on the following basis: "In *sensitivity*, the result must not be more than ten points below that of the control laboratory. In *specificity*, the result must not be lower than 99 per cent."

In the 1939 evaluation only 22 of the 41 laboratories were unsatisfactory in the performance of at least one of their tests, in contrast to the 1938 study in which 30 of 46 laboratories showed such unsatisfactory results. A few examples may be given. Whereas Kolmer showed a sensitivity by his complement-fixation test of 83.4 per cent and a specificity of 100 per cent, the laboratories in the study varied from 47.3-86.3 per cent with respect to sensitivity. None of the laboratories fell below 99 per cent in specificity. Kahn, by the use of the standard precipitation test, scored 77.4

per cent on sensitivity and 100 per cent on specificity, whereas the laboratories in the evaluation study showed results varying from 58.4-89.9 per cent in sensitivity. Two fell below 99 per cent on specificity. Kline, with his diagnostic test, scored 78.7 per cent on sensitivity and 100 per cent on specificity. The laboratories using his method varied from 71.3-90 per cent on sensitivity, and only one fell below 99 per cent on specificity.

The above results all refer to either positive or negative reactions. It is the group of blood samples reported as having doubtful reactions that may be troublesome. Kolmer had no doubtful results in either the syphilitic or nonsyphilitic groups. Some laboratories using the complement-fixation test reported a high percentage of bloods in the syphilis group as presenting a doubtful reaction. Several reported doubtful results in the nonsyphilitic group—in one laboratory as many as 7 of 114 samples. The same holds true for the Kahn standard and Kline diagnostic tests. Doubtful tests in known syphilitics may not lead to serious confusion. However, in laboratories showing many such reactions, and therefore a much lower percentage of positive results than the control laboratory, the sensitivity of the test is low. It is the doubtful tests in the nonsyphilitic group that are so troublesome to the practitioner.

### CHOICE OF BLOOD TESTS FOR SYPHILIS

Ideally the most desirable test will be that one which has the highest degree of sensitivity, the one which gives the greatest number of positive reactions in syphilitic patients, and at the same time combines with this the highest degree of specificity, i. e. gives only negative reactions in nonsyphilitic subjects. Unfortunately the physician will have practically no choice in the tests he must rely upon. In most instances he will send his blood samples to public or hospital laboratories. The laboratory director will have decided upon the type or types of tests to be used in his laboratory. Evaluation studies made nationally and intrastate as well at least play a valuable role in making the laboratory directors conscious of their shortcomings, if any.

In general, flocculation tests (Kahn, Kline, etc.) are more sensitive than the commonly used Kolmer complement fixation (Wassermann) test. This is shown quite clearly in those evaluation studies in which sera from *syphilitic patients were classified according to the stage of the disease*. With an occasional exception, the flocculation tests were more sensitive than the complement-fixation test in both primary and late syphilis. Under both of these circumstances the reagent content may be relatively low, and thus be found only by the more sensitive tests.

In all the evaluation studies, however, the Kolmer complement-fixation test was 100 per cent specific, with but one doubtful test in the sera from

syphilitic patients One author points out that it were better to miss an occasional diagnosis on a serologic basis in primary syphilis where the darkfield examination may make the diagnosis, or in late or treated syphilitic infection, than to pin a diagnosis of syphilis on a nonsyphilitic individual I am in hearty agreement with this statement In recent years Kahn has been warning against the trend of increasing the sensitivity of the tests used for diagnostic purposes

The "presumptive" and "exclusion" tests, highly sensitive tests used for "screen" purposes, are meeting opposition from several quarters It has been clearly shown that a higher percentage of false-positive reactions is obtained with these tests Their use is thus fraught with danger unless reporting is guarded in such a fashion that the practitioner unfamiliar with the purpose of the "screen" test will not mistake it for an acceptable diagnostic test Authorities also have called attention to the fact that these sensitive tests have been advanced on a false premise Experience has shown that under some circumstances sera which are negative to these "presumptive" or "exclusion" tests are not necessarily negative to the less sensitive routine tests

Attention must be given to an interesting phenomenon encountered at times This is the unexpected disagreement which may exist in the results obtained by the use of several tests on the same serum Apparently this seems to be entirely unrelated to the amount of reagin present As has been said, it is not at all exceptional to obtain positive tests with the more sensitive flocculation tests in primary or in late or treated syphilis and negative complement-fixation tests The rational explanation is that this depends upon the amount of reacting substance in the blood stream However, in contrast to such a finding one may encounter positive complement-fixation tests and negative flocculation tests even in acute syphilis This phenomenon is seen most often in patients who are under treatment or who have completed it, especially in late cases It may also occur in congenital syphilis The explanation of this unexpected serologic result has not been given as yet

Contrary to the belief of the originators of certain tests, and of directors of some state laboratories, it still seems best that all samples of blood offered for serodiagnosis be subjected to both a flocculation and a complement-fixation test The partiality of the authors for their test is understandable Laboratory directors are influenced by matters of economy into accepting only a flocculation reaction as a routine serologic test

Blood samples with low reagin titer, as in primary and in late or treated syphilis, may be detected by the use of the more sensitive flocculation test The check by the more specific complement-fixation test gives substantial assistance Thus it has been, and still is, common practice to determine

the flocculation reaction first, and, if this is positive, to check it with a complement fixation test. By this plan an apparently positive blood is checked further by the more specific, but also more time-consuming, complement-fixation test. In the long run this is an acceptable procedure, although we know that a small number of cases, in which the less sensitive test (the complement fixation test) is positive and the other more sensitive test is negative, will be missed by this plan.

## INTERPRETATION OF RESULTS

In recent years more and more laboratories are abandoning the reporting of tests as 4+, 3+, 2+, 1+,  $\pm$ , and negative, for "positive," "doubtful," and "negative." One connotation of the former method of reporting was that it represented a quantitative evaluation. Such is not the case, however, for bloods of varying reagin titer may cause complete complement fixation (a 4+ test). On the other hand, the more recently adopted method is not uniform. In some laboratories only the 4+ reaction is reported as positive and 3+, 2+, 1+, and  $\pm$  as doubtful. In others, again, the 4+ and 3+ are called positive and the rest doubtful. Speaking from experience with practitioners—not syphilologists—I believe that the method which uses only the three terms has been highly beneficial in leading to a better evaluation of a given test in individual patients. With this method of reporting a 2+ or 1+ no longer connotes a "touch" of syphilis. The very term "doubtful" has a psychologic effect on the physician, for it casts doubt upon the diagnosis. Such terminology appears to have lessened to some degree the haste with which the physician has begun treatment.

In the interpretation of reports of serologic tests, it is necessary to recall certain factors concerning the nature of the test and its technic:

- 1 The tests for syphilis are nonspecific, and yet are remarkable for the assistance they may give in diagnosis.
- 2 Biologic false positive reactions, even though few, occur in normal persons.
- 3 Certain diseases other than syphilis may give biologic false positive tests. (In the future the use of Kahn's verification test, that is, the influence of temperature upon the precipitation phenomenon, may settle these last two problems.)
- 4 The tests are performed by human beings, and therefore an infallible technic cannot be assured. The variables which may enter here are several: there may be an inconsistency in reading results with changes in personnel, errors may occur in the numbering of tubes and accompanying slips, clerical errors may play a part depending on methods used in reporting.
- 5 The rating of the laboratory is important in the evaluation of tests reported. Here certain factors must be considered, as the tests used, the

sensitivity of antigens in use, consistency of antigen sensitivity, and whether the technic of the originator of the test is followed. This may be summed up in the advice to *know the reliability of the laboratory you use*.

It should not be necessary to stress the obvious errors which may appear in the technic of collection and labelling of blood samples. Carelessness is especially likely to occur in clinics. The collection of samples of blood from several persons before attaching identifying information to the tubes is inexcusable. Mistakes in identification are almost certain to occur.

#### INTERPRETATION OF SEROLOGIC TESTS

The proper interpretation of serologic tests in untreated syphilis is possible only with knowledge of the following points:

1 In the primary stage, the blood tests may be negative at the time when the reagin is at subthreshold level. By the time the chancre has been present for two weeks, positive serologic tests will be present in well over half of the patients. In a few instances the test may not become positive until as late as two months after the appearance of the lesion. If samples are taken at intervals of several days, the reactions will develop somewhat as follows (see Table III).

TABLE III

EFFECT OF TIME UPON SEROLOGIC REACTION OF BLOOD

<i>Complement fixation Test</i>	<i>Flocculation Test</i>
Negative	Negative
Negative	Doubtful
Negative	Positive
Doubtful	Positive
Positive	Positive

2 Secondary syphilis is associated with positive complement fixation and flocculation tests in 100 per cent of cases. The writer is aware that textbooks on syphilology state that occasionally secondary syphilis is associated with negative blood tests. May some of this belief date back to days of less sensitive tests? Have all such reputed cases had more than one sample of blood tested before treatment to rule out error in the laboratory? Only recently, we saw a patient with circinate secondary skin lesions and darkfield positive genital lesions in whom the Wassermann and Kahn tests were reported as negative. A second sample of blood three days later was positive. In such an instance an error occurred in the collection or testing of the blood, or in the reporting of results of testing. One must assume secondary syphilis must have associated with it a definitely positive blood test. If I seem to deny the extremely rare instance

of secondary syphilis with a negative serologic reaction, at least I am not giving comfort to the physician who would treat the patient with pityriasis rosea as secondary syphilis, purely on a clinical diagnosis

3 Late syphilis is not consistently associated with either negative or positive reactions. The reaction varies with the amount of reagin in the blood. This has usually dropped with the passage of years. Although late benign lesions, such as gumma of skin, bone, etc., show positive tests in 90 per cent or more of cases, the reactions may be negative in both complement fixation and flocculation tests, or may be doubtful in either or both. Cardiovascular syphilis may have associated with it negative blood tests in as many as 20 per cent of the cases. In most forms of central-nervous-system syphilis, serologic tests on the blood will be positive in both types of test, although they may be doubtful or negative. On the other hand, tabes dorsalis is commonly associated with negative serologic reactions in the blood. The importance of spinal fluid findings will be discussed elsewhere.

4 In untreated latent syphilis the serologic reactions are variable. During the early years of symptomless infection the reagin titer is of such level that both complement-fixation and flocculation tests are positive. Latent syphilis of many years' duration may be accompanied by either negative or positive reactions with both types of tests. With the passage of years, however, the complement fixation test may become doubtful and the flocculation test remain positive. On the other hand, the former test may be negative and the latter doubtful, or both may be doubtful. In an occasional case the complement-fixation test may be positive and the flocculation test negative.

Obviously treatment influences the serologic reactions greatly. In all early cases, and in most other syphilitic patients, if treatment is adequate the complement-fixation test becomes doubtful at first and then negative, to be followed by a persistently positive, a doubtful, or a negative flocculation test. This common sequence is described since I find that such a course of events is not recognized by some physicians. This is because it is not practical for the man in the public clinic or in practice to take more than two or three samples of blood during a complete course of treatment. Only in highly organized clinics, usually at teaching institutions, are blood tests made at short intervals. With the examination of a dozen or two blood samples in each case during the course of treatment it is possible to note the sequence in the reversal of the tests. Occasionally, during treatment of late syphilis the flocculation test may reverse first, the complement fixation test remaining positive for a much longer time. Finally, "serofastness" may persist during treatment, that is, one or both types of tests may remain positive in spite of any amount of treatment. Then,

paradoxically, spontaneous reversal may take place in such cases in months to several years following the cessation of treatment. More space will be given to some of these points under appropriate headings in succeeding chapters.

#### HISTORY AND TEST CONTRADICTORY

*The interpretation of doubtful or positive tests for syphilis in the individual without a history or clinical evidence of syphilis* offers the physician one of his most troublesome problems. In this day of compulsory blood tests for syphilis for marriage licenses, food handlers' certificates, and a dozen and one other reasons, this perplexing problem is constantly arising.

Such cases require the utmost of care and judgment. I feel sure that the medical profession as a whole would be startled and shocked if it could see in the total, the untold misery, mental shock, and blighted lives which result annually by mismanagement of the individual having one positive or doubtful serologic test.

Just the day before this was written such circumstances were brought home to me. A young white woman appeared in the clinic emotionally disturbed. A local physician some days before had had a sample of her blood examined as required for a food-handler's certificate. Only one Kahn test was done, whether the result was doubtful or positive is not known. She was told she had syphilis, and needed treatment. The history revealed a stout denial of any intimacies with men other than kissing, and nothing suggestive of acute syphilis. She demanded treatment in spite of our advice for examination and another blood test. Her mind was fixed on treatment. She returned to her physician, and in a telephone conversation an hour later it was learned that she had received an injection of neoarsphenamine. A young woman was thus started on a path of syphilophobia and antisiphilic treatment, in spite of a negative story of sexual exposure, a negative history, and one presumably positive flocculation test!

Such hasty action cannot be condoned under any circumstances. Other than in the state of acute syphilis the disease is never an emergency, and therefore immediate treatment is not urgent.

At times we are forced to make the diagnosis of syphilis on serologic tests with a negative history and physical examination. In the presence of a persistently and repeatedly positive serologic reaction with two types of tests (complement fixation and flocculation), the diagnosis of syphilis is acceptable. In the clinic at Vanderbilt University Hospital such serodiagnoses are made.

The most frequent problem causing hesitancy in the serodiagnosis of syphilis is the report of only one positive flocculation test, or a doubtful complement-fixation test in the absence of a history of syphilis or any clinical evidence of such infection. Such a patient is never labelled syphilitic.



in our clinic without some additional evidence. The evaluation of such a case, involving a bringing together of all possible collateral evidence, often entails days or weeks of study. We rather expect that the average physician will think nothing of spending weeks in working out the diagnosis in obscure gastro-intestinal disease, neurologic disease, or hematologic problems. Yet patience seems to leave him immediately when he is confronted with a positive blood test for syphilis. The physician usually gives no thought to the possible sources of collateral information which may be plumbed for an explanation of positive tests.

Assistance in the evaluation of questionable serologic evidence may be gained by investigation along the following lines: from the history and physical examination, whose importance in establishing the diagnosis of syphilis have been stressed in Chapter III. The blood should be repeatedly examined in more than one laboratory, and by different types of tests. Discrepancies from time to time in the same laboratory and between laboratories should make the attending physician wary of the diagnosis of syphilis. The value of spinal fluid examination is apparent since in asymptomatic neurosyphilis the flocculation test only may be positive or doubtful. As was indicated in Chapter III, and earlier in this chapter, certain nonsyphilitic diseases may cause false flocculation tests. A realization of this fact should lead to such laboratory studies as may be indicated to rule out diseases which may give false positive serologic tests.

Although the demonstration of negative blood tests for syphilis in a marital partner proves nothing, positive tests in the partner may have significance in the interpretation of the doubtful or positive flocculation test in the patient. The demonstration of syphilis in parents may explain the positive or questionable blood test in a young person. Even extra marital sex contacts, if of long standing liaisons, may be worthy of examination.

These various methods are employed in our clinic in the evaluation of tests for syphilis which are not consistently or repeatedly positive.

Other facilities for more detailed serologic study may not be available to the reader, but should be mentioned because they are acquiring more prominence in the literature. Kahn's verification test, a precipitation test related to temperature as noted earlier in this chapter, may prove to be invaluable in the future. Quantitative tests may be of assistance in an evaluation of the questionable cases. False positive reactions probably will be associated with low or falling titers. Positive tests due to syphilis will probably show a higher titer or a titer maintained at a fairly constant level.

The following case represents an example of the problems which may arise in serodiagnosis and which often require prolonged study.

**Case 3.** A confrere in his late twenties consulted me because of variable results in a series of serologic tests for syphilis. His position was such that he was required to have serologic tests at intervals. These had been negative for five years before I saw him. The last one had been done eighteen months before, and was reported as negative in both the Wassermann and the Kahn tests. He came to me with an array of reports, as listed below, to which we added more. There was no history of syphilis. He had married eighteen months before he consulted me. His wife's blood tests were negative on several occasions.

<i>Month</i>	<i>Place</i>	<i>Unknown Test</i>	<i>Wasser- mann</i>	<i>Kahn</i>	<i>Kline</i>
March	A state laboratory	—	Doubtful	Negative	Positive
April	A state laboratory	—	Negative	Negative	
June	A private laboratory	Positive			
June	A private laboratory	Positive			
August	A state laboratory	—	Doubtful	Negative	Positive
August	(Spinal fluid negative)				
October	Vanderbilt University Hospital	—	Negative	Negative	
October	Vanderbilt University Hospital	—	Negative	Negative	
October	Tennessee State Laboratory	—		Negative	
December	Tennessee State Laboratory	—		Negative	
December	Vanderbilt University Hospital	—	Negative	Negative	

**Comment.** Obviously no treatment was given. The only known possible factor which could have contributed to this doubtful serologic picture was experimental immunization for yellow fever which had been carried out in either January or February before the required periodic blood test was reported as noted above.

No definite rules can be set up to answer all problems which may arise in the field of serodiagnosis in syphilis. Each case has to be decided upon its own merits. Furthermore, the practitioner must, as in every field of medicine, rely upon his judgment in making his decision. Probably in many instances no two syphilologists would arrive at the same plan of management in a given case. Broadly our cases are interpreted with necessary variations, somewhat as follows. (These interpretations presuppose a negative history of syphilis or previous antisyphilitic treatment, a negative physical examination for syphilis, and a negative spinal fluid. They also imply either negative results in the examination of family or sex contacts or the unavailability of such for examination. Furthermore,

there must be no evidence of disease capable of giving false positive results )

1 Persistently and repeatedly positive reactions with both complement-fixation and flocculation tests are accepted as establishing the diagnosis of syphilis

2 Persistently and repeatedly positive flocculation tests with doubtful complement fixation tests are considered to mean syphilis, especially in the presence of admitted and repeated sexual exposures

3 Persistently and repeatedly positive flocculation tests with negative complement fixation tests are accepted as indicating syphilis in persons who have been sexually promiscuous for years (*Partial seroreversal may take place spontaneously with the passage of a decade or more*) In virgins and in those denying sexual exposure observation and prolonged study of the serologic reactions for syphilis is indicated

4 Fluctuating flocculation tests with possibly an occasional doubtful complement fixation test thrown in, cannot be accepted to mean syphilis

Only by careful observation and the avoidance of haste can one avoid unfortunate instances, as in the following case studied in the Vanderbilt University Hospital Syphilis Clinic

**Case 4** A young woman, unmarried and pregnant, was admitted to a hospital for delivery Her blood on admission was said to be Kahn positive A healthy baby was born. Blood from the umbilical cord gave a positive Kahn test The mother received three injections of neoarsphenamine and the child some stovarsol The mother's blood was then found to be negative

When she was seen first by us she suffered from a distressing syphilophobia The baby had been examined by several pediatricians, and later was studied in the Vanderbilt University Hospital Pediatric Clinic with negative findings as regards syphilis The patient herself had had one spinal fluid examination and numerous blood tests at the hands of several private physicians Blood Wassermann and Kahn tests and spinal fluid examination in the Syphilis Clinic were negative, as was the physical examination

Since we had to accept the original Kahn test at time of delivery at its face value, and admit she might have just become seropositive in early syphilis, with rapid reversal by three injections of an arsenical, we urged investigation of her one and only contact This was a married man with whom she had held a rendezvous two or three times a month for several years He had a wife and several children, apparently healthy Since he was a citizen of good standing the patient refused to divulge his name However, she discussed the situation with him upon our advice, and he consulted a private physician who found him to be seronegative

**Comment.** This represents an instance of syphilophobia in a woman who not only feared for herself but also for her child, merely because a physician was

too hasty in treating "a reacting substance" in the blood of a pregnant woman which was transferred to the child, as demonstrated by testing the cord blood

## SUMMARY OF BLOOD SEROLOGIC TESTS

In summary, one may say that although the development of the serologic tests for syphilis has given us the most valuable assistance in the diagnosis of syphilis, it has led to much which is unfortunate. It can never be known how much morbidity has been caused by the use of arsenic in the treatment of persons not syphilitic, nor how much suicide or syphilophobia. Nor can it be estimated how many families have been broken up nor how many affianced couples have become estranged through lack of the proper interpretation of reports of a test so nonspecific that the antigen used is not even remotely related to syphilis.

## EXAMINATION OF THE SPINAL FLUID

The study of the spinal fluid is an essential part of the examination and general evaluation in every syphilitic patient. There are few exceptions to this statement. The importance of the spinal-fluid findings in the diagnosis and prognosis of syphilis will appear time and again in the succeeding chapters. Several tests should be carried out for a complete study of the fluid, only one, however, is actually specific for syphilis—the Wassermann test. The remainder may be modified by any one of a number of pathologic states in the central nervous system.

### SPINAL-FLUID CONSTITUENTS

**Proteins.** In the normal person the choroid plexus, which presumably is the site of spinal-fluid production, is not permeable to the proteins of the blood. Thus the normal fluid is essentially a protein-free filtrate of the blood serum. In inflammation of the meninges, permeability to serum proteins develops. Whereas 15–45 mg per 100 cc of fluid constitutes the limits of normal protein concentration, in central-nervous-system syphilis the protein content may vary from the normal limits to 200 mg per cent or more, the quantity depending upon the type and degree of pathologic change. The protein in the spinal fluid is chiefly a globulin.

Testing for globulin in the spinal fluid is commonly done by one of three tests—the ammonium-sulphate test, the butyric-acid test, or the phenol test. (The technique of these simple tests may be found in any of the textbooks on laboratory procedures.) At Vanderbilt University Hospital the ammonium-sulphate test is used since it is less sensitive, and therefore associated with fewer false-positive reactions. Quantitative tests for protein are usually not carried out in state laboratories or in routine examinations for changes in the spinal fluid in syphilis, and thus will not be discussed.

**Cells** Normally the spinal fluid contains from 80-7 lymphocytes per cu mm. of fluid. In active syphilitic inflammation, the cell content may vary from the normal number to as many as eight hundred or more cells per cu mm. Syphilitic inflammation is usually associated with a lymphocytic reaction. Only in a very active, acute process, as in acute syphilitic meningitis, may some polymorphonuclear cells appear. Cells in the spinal fluid are counted in a counting chamber as in the method of making white blood counts, except that a different dilution is made in the pipette because of the few cells. (See a laboratory manual for this examination.)

#### COLLOIDAL TESTS

The colloidal gold test, introduced by Lange, was the first of these to be described. Because of certain technical difficulties in the preparation of the gold solutions, the mastic test has superseded the original gold test in many laboratories. The exact nature of the reaction in the colloidal test has not been satisfactorily explained. It is definitely related to the increase in proteins in the fluid, but apparently not necessarily in a quantitative fashion. It seems probable that the changes in the colloidal test rest upon the proportions of several proteins which may be present, and their interrelationships. In either test, to varying dilutions of the spinal fluid are added gold or mastic solution, as the case may be. The degree of change is recorded numerically, with 5 representing the maximum change and so on down to 0. Thus decolorization in the gold test and complete precipitation with the mastic solution is rated as 5. In the gold test the pattern of the parietic curve is described as 5555432100, that of the tabetic curve in general as 0012343210, and that of the meningitic curve as 0000234420. (These examples indicate the pattern of the zone reactions. They naturally vary from case to case.) The only one of these curves of diagnostic and prognostic importance and of any degree of consistency is the first or parietic curve. The others are mentioned only because questions are frequently asked concerning them. The mastic curve especially is less likely to show the differentiation into the three types, but it does give a clear-cut parietic curve. The details of the technic of the colloidal tests may be found in the various books on laboratory methods.

#### SEROLOGIC TESTS

The only test done on the spinal fluid which is specific for syphilis is either a flocculation test (Kahn test, and the like), or the complement-fixation test (Wassermann test), as in the case of the blood tests. It appears from several studies that the flocculation tests are not so sensitive in the spinal fluid as is the Kolmer modification of the Wassermann test. Thus and other technical reasons make it safe to say that at the present date the

Wassermann test is preferable to a flocculation test in the study of the spinal fluid, the opinions and comments of the authors of various flocculation tests to the contrary notwithstanding. Some degree of quantitation of reagin in the spinal fluid is of great value not only from the viewpoint of diagnosis and prognosis, but also relative to the results of treatment as may be seen in some of the case reports in Chapter xii. It is therefore customary to do the serologic tests with several different dilutions or amounts of spinal fluid.

#### SIGNIFICANCE OF SPINAL-FLUID ABNORMALITIES

The variety of spinal-fluid abnormalities that may occur in the several forms of neurosyphilis will be indicated in the later chapters on clinical syphilis.

At this point only a few statements are necessary as to the general significance of abnormal findings in the spinal fluid. An increase in the protein content of the spinal fluid merely means increased permeability of the meninges, and thus will be seen in meningeal inflammatory reactions of whatever etiology. It may also occur in the presence of tumours as well as in infections. Cellular increase in the spinal fluid also is an accompaniment of inflammation of whatever etiology. The type of cell varies, however. Thus the coccus and bacillus infections usually call forth a polymorphonuclear cellular response. Inflammation due to the *T pallidum*, the tubercle bacillus, and the viruses shows a predominantly lymphocytic reaction. Tumours may have an associated lymphocytic response. The colloidal tests may show changes in any type of meningitis, virus infections, and in multiple sclerosis.

For practical purposes it may be accepted that a positive serologic test on the spinal fluid means an invasion of the tissues of the central nervous system by the *T pallidum*. (In fresh fluids the report of an anticomplementary reaction is accepted as being of the same significance as a positive test. This is not true of old fluids.)

*False-positive Wassermann reactions* in the spinal fluid have been reported in a few diseases. Kitchen, Webb, and Kupper in their study of the blood tests during active malaria studied the spinal fluid in four cases. In one patient, the spinal fluid showed 28 cells per cu mm and a strongly positive Wassermann reaction on the fifteenth day of the infection. The fluid was negative before and after this time. Another author reported a patient who complained of nausea, vomiting, and a stiff neck. The spinal-fluid Wassermann was positive. The blood tests for syphilis were negative. Some days later tertian-malaria parasites were found. Then the blood Wassermann became positive. After treatment with quinine, the blood became negative and the spinal fluid later was found to be negative on two

occasions. The spinal fluid has been found positive to flocculation tests in yaws. Two Chinese authors, in a study of falsely positive blood tests for syphilis in relapsing fever, found that of sixteen patients in whom the spinal fluid was studied, nine showed transient but clear-cut positive tests. The fluids showed increased globulin, cells, positive serology, and negative colloidal tests. Upon inoculation into squirrels five of six of these spinal fluids were shown to contain the organism of relapsing fever. McLean and Munger reviewed the literature and found reports of thirty-two falsely positive spinal-fluid serologic reactions for syphilis in the presence of tumours in the central nervous system. In twenty-five of these there was no clinical or pathologic evidence of syphilis. They reported eight additional instances of false-positive tests in the presence of various surgical conditions of the central nervous system in all of which subsequent tests were negative.

**Blood in the Spinal Fluid.** In the presence of a bloody spinal tap, positive serologic tests or other abnormalities cannot be accepted as significant. Globulin tests may be positive, the cell count may be increased due to blood cells, depending upon the amount of contained blood. Several observers have shown that a very small quantity of serum from blood giving positive serologic tests, when added to negative spinal fluids, provides enough reagin to give positive tests. It thus becomes apparent that in a patient having positive blood tests, only a negative reaction in a bloody spinal fluid can be of significance. In patients having a seronegative blood but with blood in the spinal fluid, a positive Wassermann test on the spinal fluid may be accepted as being significant.

In concluding this chapter, it may be worthy of comment that the serodiagnosis of syphilis is not necessarily simple. As with all laboratory procedures used in the practice of medicine, the interpretation of the reports from the laboratory must be related to the clinical picture in the given case. In the last analysis this depends upon the experience and judgment of the physician.

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## THERAPEUTIC AGENTS AND METHODS USED IN ANTISYPHILITIC TREATMENT— CONTRAINDICATIONS AND UNTOWARD EFFECTS

### HISTORICAL NOTE

SHORTLY after the recognition of syphilis as a disease in the early part of the sixteenth century, a wood known as "guaiacum" among the Indians was introduced into Spain for treatment of the "French disease." Holcomb believes that the use of guaiacum is the basis for the belief that syphilis had its origin in America. He points out that at that time it was common belief that, through Divine Providence, a curative herb existed for each disease. Since guaiacum grew in the Western Hemisphere and was supposed to be effectual in the treatment of syphilis, it was used as proof that syphilis had its origin in the Americas. In Europe guaiacum was called Holy Wood (Holcomb, "The Holy Wood and the Hainan Myth of the Origin of Syphilis," Science Press, 1938).

Mercury had been used in ointments for skin diseases from the time of the Middle Ages. It was introduced into Europe from Arabia. Its use for syphilis was mentioned in Fracastorius' poem. The metal was used not only in ointments but also as fumigations. Hot baths and steam chests were often used in conjunction with mercury therapy.

Wallace of Dublin introduced the use of iodides in the treatment of syphilis about a century ago.

Other than the use of many herbs at one time or another, mercury and iodides provided the chief remedies for the treatment of syphilis until the introduction of arsphenamine ('606') by Ehrlich in 1910. This opened the era of arsenotherapy.

Although bismuth was used as early as 1889 by Balzer, it was not generally accepted at that time. Sazerac and Levaditi revived the use of this metal in 1921-1922. Within a decade it had practically replaced mercury as the heavy metal of choice in syphilotherapy.

In the treatment of syphilis the physician's therapeutic armamentarium contains several basic chemicals, as well as fever produced by one of several methods. Either form of treatment under certain circumstances may lead to untoward reactions, even death, and therefore their use at times may be contraindicated. Some circumstances may place before the physician a difficult problem in the choice of therapy.

The objectives of this chapter are to give a brief description of therapeutic methods, a statement of their efficacy and indications under varying circumstances, and the possible untoward results from their use as well

as the contraindications to their employment. Dosage will be given, as well as a word as to the preparation of drugs. Little space will be given to the voluminous literature concerning the pharmacologic action of the antisyphilitic agents. Those especially interested in this subject should consult the many original sources and textbooks on pharmacology.

The evaluation of the efficacy of antisyphilitic drugs has usually been based on laboratory and clinical studies. Laboratory studies include the prophylactic use of drugs in rabbits. Furthermore, the efficiency of the drug is judged by its action in causing (1) the disappearance of treponemata from the syphilitic lesions, (2) the healing of such lesions, and (3) the prevention of relapse.

If experimental studies in rabbits indicate some degree of therapeutic efficacy and if the toxicity is limited, drugs are usually given an experimental clinical trial in human syphilis. In addition to a study of the toxic effects of new drugs, certain observations must be made relative to their therapeutic efficacy. These studies usually include the following: (1) the rapidity with which *T. pallidum* disappears from acute lesions, (2) the rate of healing of the acute lesion, (3) the effect of the drug on the serologic tests—the rapidity with which a positive blood becomes negative, (4) the incidence of abnormal spinal fluid findings in the early stages of syphilis during the time the experimental drug is being given, (5) the incidence of clinical relapse, during the course of, or subsequent to completion of treatment, and (6) the development or lack of development of the late manifestations of syphilis.

These points are set forth so that the practitioner may understand the prolonged study which is necessary in the evaluation of any new drug. At least five years must elapse subsequent to treatment before a final estimate of a new drug can be made. If the physician will keep these facts in mind he will use greater discretion in the choice of treatment, and he will use the tried methods in spite of the appeals of the pharmaceutical "detail man." The general practitioner should leave the study of new drugs to the personnel of well-organized clinics, where controlled observations can be made in adequate volume.

Time and experience have shown that a combination of arsenic in one of its forms and a heavy metal offer a chemotherapeutic mode of attack which gives the best results. The details of their combined use will be given in the chapters dealing with the several phases of clinical syphilis. The relative potency of the chemicals effective in the attack upon the *T. pallidum* is generally rated as follows, the most potent having a value of 10: trivalent arsenic 10, bismuth 8, and mercury 4.

## THE ARSENICAL PREPARATIONS

After prolonged study, Ehrlich prepared an organic arsenical compound that was spirochetocidal and yet of such low toxicity that it could be given to the host with safety. Thus arsphenamine, or "606" (which indicated the number of organic arsenic compounds studied), was the first of a line of arsenical drugs developed for use in the treatment of syphilis. Subsequently various preparations of arsenic have been produced in the hope of increasing the ease of administration, reducing untoward reactions, and improving therapeutic efficiency.

There are various theories as to the mode of action of the arsenic compounds on the *T. pallidum*. These drugs kill the organism, but the exact manner in which this is accomplished is not known. Some theories maintained that this group of drugs affects the host's immunity mechanism, stimulating resistance or mobilizing body defence. It has been thought by some investigators that the drugs may affect the organism in some fashion so that the host's defence mechanism can handle the resulting relatively avirulent organism. Vogtlin and his collaborators have felt that arsphenamines are not effective in their injected form, but are oxidized, and that the product, arsenoxide, constitutes the potent agent. This substance, which has an affinity for certain sulphur compounds important in cellular metabolism, is a biologic poison. Although, in the past, it has generally been accepted that the unchanged arsphenamines are not directly lethal to spirochetes, Eagle and his co-workers recently have demonstrated to their satisfaction that arsphenamine and arsenoxide (mapharsen) are directly spirochetocidal *in vitro* in concentrations usually obtained in the human being in therapeutic doses. These results have not been verified by other students.

## SUMMARY OF THERAPEUTIC ACTION

The therapeutic effect of the administration of trivalent arsenical drugs in early syphilis may be summarized as follows. The surface treponemata usually disappear from chancres or moist secondary lesions within twelve to twenty-four hours. Chancres heal in a few days after an injection, whereas secondary lesions heal after two or three injections at five-day intervals. Serologic reversal depends to some extent upon the duration of the positive reaction. In chancres, where the blood has just become positive, one injection may reverse the blood, otherwise three weeks or longer may elapse before the blood becomes negative. In secondary syphilis the change from a positive to a negative blood test commonly occurs within sixty days, but may be prolonged to ninety days and even longer.

In late syphilis arsenic therapy is measured by the healing, within a few

weeks, of late benign lesions, such as those of skin or bones, and in the reversal of the blood tests. The latter is extremely variable since sero-reversal may occur in one or two months, or not at all.

#### PHARMACOLOGY OF ARSPHENAMINES

A brief outline of the pharmacologic features of the arspenamines is necessary as a background for an understanding of their use and their by-effects. After a single dose of an arspenamine is administered intravenously, the unchanged drug appears in the urine in five or ten minutes and may do so for some four to five hours. Subsequently arsenites and arsenates are excreted in the urine for some days. Greater amounts appear in the bile and feces. Arspenamine leaves the bloodstream in a few hours to be stored as an arsenical salt in kidneys, liver, spleen, bone marrow and skin for as long as two weeks. We have found that arsenoxide (mapharsen) and clorarsen, a new drug closely allied to it, are removed from the bloodstream within fifteen minutes after injection.

Because of the incidence of neurosyphilis, information relative to the penetration of arsenic into the central nervous system should be of importance. No conclusions can be drawn from the demonstration of arsenic in the spinal fluid as to the therapeutic efficacy of a given preparation. It has been shown that about three fourths of patients receiving an arspenamine have arsenic in the spinal fluid subsequently, and after the use of pentavalent tryparsamide arsenic is found in the spinal fluid in 100 per cent of cases.

The organic arsenic compounds may be divided into two groups: the trivalent, and the pentavalent. The former are used in all forms of syphilis, the latter have special uses to be brought out below.

#### TRIVALENT ARSENIC PREPARATIONS

The following forms of trivalent arsenic are in common use.\*

**Arsphenamine** This was Ehrlich's original "606" or "salvarsan." Its arsenic content is 30-32 per cent.

**PREPARATION** In a glass container are placed 10 cc of distilled water for each 0.1 Gm of drug to be used. The drug is sprinkled into the water and may be stirred into solution. Sodium hydroxide (usually 4 per cent) is then dropped into the solution until the precipitate which appears is dissolved. The drops should be counted. Solution of the precipitate may be obtained by stirring gently (without mixing air into the solution), or by rotation of the container.

\* Never make up a solution of an arsenical drug before carefully reading the label on the ampule. Thus errors which have been known to be fatal can be avoided. Ampules which are cracked should be discarded. This is likewise true of those in which the powdered preparation is lumpy and in which there has been a change from the usual colour.

After the precipitate has completely dissolved, an excess of alkali is added to the extent of one fourth of the amount originally used. The solution is then diluted with water so that the volume will be 25 cc per 0.1 Gm of drug. It is then filtered. After standing one-half hour it is ready for use.

**DOSAGE** The dose of arsphenamine is roughly based on 0.1 Gm per 35 pounds of body weight, thus making the average dose for women about 0.3 Gm and for men 0.4 Gm. Courses usually consist of six to eight injections at weekly intervals. In large, muscular, healthy young men with acute syphilis, doses of up to 0.6 Gm may be indicated. The drug is given intravenously slowly, and usually by the gravity method.

**USE** The authorities most prominent in syphilology almost universally agree that arsphenamine is the most potent of the arsenic preparations. With its use the results in acute syphilis are superior to those obtained with other trivalent arsenical drugs. In the Vanderbilt University Hospital Syphilis Clinic arsphenamine has been the drug of choice in acute syphilis, in treatment resistant acute syphilis, in syphilitic iritis, and in certain forms of neurosyphilis where treatment with trivalent arsenic is employed. Practically all syphilologists speak only in terms of arsphenamine in the treatment of syphilis and will concede little to the newer forms of arsenic in early syphilis. I believe we must be practical in the matter, however, and recognize the fact that the majority of syphilitic patients in the United States are to be treated by either general practitioners or the personnel of the public health clinics. The use of old arsphenamine under such circumstances is impracticable, and this fact might as well be faced.

**Neoarsphenamine** This drug is also known as 'neosalvarsan'. The arsenic content is about 20 per cent.

**PREPARATION** This light yellow powder is readily soluble in small quantities of distilled water, producing a yellow solution which is neutral and ready for use. Because oxidation occurs upon standing, the drug must be administered within twenty minutes of its preparation. (Multiple doses should be made up only in clinics where patients are treated in rapid succession.) The enhanced toxicity due to oxidation also forbids drawing the solution into the syringe and expelling it to hasten solution of the powder.

Into a sterile beaker are placed 10-20 cc of *cool* distilled water. (The volume of solution varies with the dosage, 0.6 or more Gm neoarsphenamine may safely be given in 20 cc of water.) The ampule is opened and the powder is *sprinkled* into the water. Sprinkling the powder into the water usually permits the drug to dissolve without the need for agitation. If some agitation is necessary it may be accomplished by rotating the beaker. If a clear solution is not obtained it should be discarded and a new one made. The solution is drawn into a 20-cc syringe, and is administered intravenously, using at least three to five minutes for the injection of the larger doses.

**DOSAGE** The dose of neoarsphenamine may be roughly estimated as about

0.15 Gm. per 35 pounds of body weight. As in the case of old arsphenamine, smaller doses are usually given to women than men. For patients of average size, doses of 0.45 Gm. for women and 0.6 Gm. for men are used in the treatment of late latent or late benign syphilis. In acute syphilis and in trivalent arsenical therapy as used in neurosyphilis, a full dose of the drug should be used. In large muscular young men with acute syphilis doses up to 0.8 or 0.9 Gm. may be used on a basis of weight. In persons never having had arsenical therapy before, it may be wise to make the first dose smaller than that planned for subsequent use. Age and debility may necessitate smaller doses. In acute syphilis and in neurosyphilis a course should consist of eight to ten weekly injections, in latent and late syphilis, the courses may be shortened to six to eight injections.

**USE** Neoarsphenamine has been the drug of choice for office practice and in the clinic for the treatment of syphilis irrespective of the stage of the disease. It is advantageous because it readily can be made into a solution which can be administered by syringe. Since it is not so efficient as arsphenamine in the treatment of acute syphilis, longer courses of neoarsphenamine should be used.

In the treatment of late latent syphilis and late benign syphilis and in uncomplicated aortitis, neoarsphenamine is probably just as efficacious as arsphenamine. It is rather difficult to obtain clear-cut data upon this point, since most of the published data of the Co-operative Clinical Group consists of that collected during the times when old arsphenamine was the drug in common use. In a study of over five hundred cases of latent syphilis, in which we compared arsphenamine and neoarsphenamine for their effect as measured in seroreversal and serorelapse, we found that the latter drug seems to be as efficient as the former.

**Mapharsen** Arsenoxide was known to Ehrlich, but was found to be too toxic for use in the human being in the amount used. This oxidation product of the arsphenamines is thought to be the active therapeutic agent against *T. pallidum*. The arsenic content is about 29 per cent.

**PREPARATION** This white powder dissolves in small quantities of water. The volume of the solution should not exceed 10 cc. even for the larger doses. (It may stand for longer periods of time than neoarsphenamine before using.)

The desired amount of sterile distilled water is placed in a sterile beaker or medicine glass. The ampule is opened and the drug is sprinkled on the water. It dissolves rapidly. It may be agitated and mixed with air to hasten solution without increasing its toxicity, in fact, the solution should be aerated by drawing it into a syringe and expelling it. The solution is drawn into a 10-cc. syringe and is given as rapidly as possible, thereby reducing the possibility of pain along the course of the vein.

**DOSAGE** Mapharsen is used commonly in dosages of 0.04 and 0.06 Gm. Since it is relatively nontoxic it is not necessary to be as careful with respect to overdosage as in the case of the arsphenamines. To put it another way, if on a

basis of sex and weight one might be hesitant to raise a neoarsphenamine dose from 0.45 to 0.6 Gm. such hesitancy need not be so great to increase the mapharsen dose from 0.04 to 0.06 Gm. In acute syphilis, central nervous system syphilis, and pregnancy the larger dosage should be employed except in very small or malnourished persons. In large muscular men with acute syphilis 0.08 Gm. should be used. Depending upon the stage of the disease it is used in courses of six to ten weekly injections. The longer course is essential in early syphilis.

**USE** Mapharsen is rapidly becoming the drug of choice for use in the office and clinic. It has all the advantages of neoarsphenamine with regard to ease of preparation and administration. It has the further advantages that standing and aeration do not increase toxicity. In the event of tissue infiltration with the drug there is much less danger of sloughing of tissues. The greatest argument in favour of mapharsen is that, other than for gastro intestinal reactions and pain on injection, it is practically free of those untoward severe reactions which may be associated with the use of the arsphenamines. Nitritoid reactions have not been reported with its use. The user of mapharsen must appreciate that he is using a drug whose efficacy has not been as indubitably established as has that of the arsphenamines for all forms of syphilis. It is still more or less in the experimental stage. In general it is agreed that arsenoxide is effective in acute syphilis. Measured in terms of the disappearance of the treponemata from acute lesions and their healing, it is probably superior to neoarsphenamine, standing between old arsphenamine and neoarsphenamine in this respect. At the present time nothing definite is known with regard to the efficacy of the drug in late syphilis, and especially in neurosyphilis. Because of its low toxicity, mapharsen has been the drug of choice in the experimental 'massive dose' treatment of syphilis.

**Clorarsen** This new arsenical has not yet been accepted by the Council on Pharmacology and Chemistry of the American Medical Association. Recently it has been given a trial, however, in several syphilis clinics in this country. It is probably converted to arsenoxide after injection. Though the drug has not been studied extensively as yet, it apparently will be found to be as effective as mapharsen. It is relatively nontoxic. We have used clorarsen for eighteen months and have given several thousand injections of the drug. None of the severe untoward reactions of arsenotherapy has been encountered. Disappearance of *T. pallidum* from acute lesions and seroreversal have been prompt.

**Silver Arsphenamine** The exact chemical nature of this compound is not known. It contains 19 per cent arsenic and 12.5 per cent silver. Since it is used rarely, only a mention will be made of it.

**PREPARATION** The dark brown powder dissolves quickly in water. As in the case of neoarsphenamine, the drug must be allowed to dissolve without agitation and aeration, and must be completely dissolved, producing a dark brown solution. Twenty minutes is the maximum time it can be allowed to stand before it is slowly injected by the syringe method.

**DOSAGE** It is given in doses of 0.1-0.4 Gm., the latter being comparable to 0.6 Gm. of neoarsphenamine. Courses of six to ten doses are used.

**USE** Although some have felt that silver arsphenamine may have a place especially in the treatment of neurosyphilis, it offers no advantage over neoarsphenamine except that no odour is noticeable to the patient and there seem to be fewer nitritoid reactions. Thus the drug has been used as an alternate in patients who cannot take old arsphenamine or neoarsphenamine. In the past it was used quite frequently for this purpose in the Vanderbilt University Hospital Syphilis Clinic, but now has been replaced by mapharsen or clorarsen as alternate drugs. Argylia may be produced by its use.

**Sulfarsphenamine** This contains 19.24 per cent of arsenic. The solution may be given intramuscularly and thus may be used where intravenous injections are impossible. It is a dangerous drug for use in adults, however.

**PREPARATION** The orange yellow powder dissolves readily in water, and is injected in a concentrated solution. Therefore 0.3 cc. of distilled water per each decigram of drug to be injected (0.9 cc. water for a 0.3 Gm. dose) is placed in a 2-cc. syringe. The ampule is opened and the water emptied into the ampule. The solution is withdrawn into the syringe, and given intramuscularly into the buttock.

**DOSAGE** The maximum dose of this toxic drug should not exceed 0.4 Gm. In adults of average size it is used in 0.2-0.3 Gm.

**USE** This drug can be used only for intramuscular injection in adults. It is a favourite drug in the treatment of infants, who seem to tolerate it without reactions. (See Chapter xiv.) In adults it should not be used except in instances where arsenic therapy is essential and intravenous injections cannot be given. The dangers of exfoliative dermatitis and blood dyscrasia in adults are twice that encountered with the other arsphenamines. Therefore it is a drug that is used as a last resort. Courses should consist of only six to eight weekly injections.

**Bismarsen** This contains 12.15 per cent of arsenic and 23.25 per cent of bismuth. It must be given by intramuscular injection only.

**PREPARATION** The yellowish brown powder dissolves easily in small quantities of water. Distilled water, 1.175 cc., is drawn into a 2-cc. syringe. The ampule is opened and the solution prepared in the ampule as in the case of sulfarsphenamine. Injection is made intramuscularly into the buttock.



**DOSAGE** This drug is used in 0.1 and 0.2 Gm. doses, the latter being the usual one for adults. Bismarsen must be used at shorter intervals than one week, and is therefore given at three- or four-day intervals in acute syphilis. Courses should consist of at least twenty injections, and Stokes recommends as many as forty injections in a course in early syphilis.

**USE** The drug cannot be used to replace the commonly accepted drugs in the treatment of syphilis. However, it is a preparation to be kept in mind for use under certain circumstances, for example, in patients in whom intravenous therapy is impossible.

#### PENTAVALENT ARSENICALS

**Tryparsamide.** The arsenic content is 25 per cent. This is an arsenical preparation of low toxicity, is weakly spirochetocidal, but is very effective in neurosyphilis. Practically its only toxic effect is upon the optic nerve, impaired vision or even blindness may occur. It has an excellent tonic action and patients often gain weight while under treatment.

**PREPARATION** The white powder is added to 15-20 cc. of distilled water in a sterile beaker or medicine glass. Its toxicity is not increased by standing or aeration as by shaking. The solution is administered by syringe, the speed of administration being of no importance in the case of this drug.

**DOSAGE** The dose is 1-3 Gm., the usual adult dose being 3 Gm. It is given in courses of twelve to twenty weekly injections.

**USE** Tryparsamide is limited in its use to neurosyphilis, because of its low treponemocidal value in other forms of syphilis. Since it is relatively nontoxic it may be used under almost all circumstances. It may be used in patients who have had arsenical dermatitis from trivalent arsenical drugs. *The one contraindication* to its use is syphilitic involvement of the optic nerve. Impaired vision may be aggravated to the point of blindness. Because of its possible toxic effect upon the optic nerve, every patient should have a prior examination by an ophthalmologist for evidence of optic nerve disease. This should include examination of the nerve head and visual fields, the latter as a basis for subsequent comparison in the event of untoward symptoms.

Tryparsamide is used in neurosyphilis where trivalent arsenic is not effective in altering either the clinical picture or the spinal-fluid abnormalities. It is used as follow-up therapy to fever treatment, and as treatment of second choice in general paresis if fever is contraindicated.

**Stovarsol** This drug, which contains 27 per cent of arsenic, is also known as acetarsone. In the adult and in older children, stovarsol is not tolerated well and therefore its use in this country has been limited to the treatment of syphilis in infants. For the preparation and dosage see Chapter XIV.

## CONTRAINDICATIONS TO THE USE OF THE ARSENICAL PREPARATIONS

Except for a few specific circumstances under which arsenical drugs should not be used, they may be employed in most cases of syphilis

**Allergy** In persons subject to allergic manifestations such as asthma, the arsphenamines may produce a nitritoid reaction It may be preferable to use arsenoxide in these cases because such reactions occur rarely, if ever, with this drug The same is true of fibroid tuberculosis

Tuberculosis as a rule is not a contraindication to the use of arsenic It is best not to use the maximum dose, however, though I believe mapharsen is safe in such dosage However, I do not believe that the tuberculous patient with an extensive exudative process who is debilitated and has fever should receive arsenic In late or latent cases of syphilis with tuberculosis it is best to use bismuth in a prolonged course, and then small doses of arsenoxide

Hypertension is not of itself a contraindication to arsenic therapy Cardiovascular disease of syphilitic origin is, as a general rule, a contraindication to the use of arsenic This will be discussed further in the chapter on this manifestation of syphilis Nonsyphilitic heart disease may be a contraindication to arsenic therapy In congestive failure this group of drugs should not be used The injection of colloidal solutions may have an untoward effect upon the damaged myocardium Repeatedly, in hypertensive and arteriosclerotic heart disease without hypertension I have seen that the injections of arsenic have apparently produced angina pectoris Therefore, I believe the initial dose should be small, as a test Subsequent doses may be increased Arsenoxide may be preferable in these cases

Though a few casts may appear as evidence of renal irritation following the injection of arsenic, repeated studies have never shown any impairment of renal function in normal persons Nephritis, acute or chronic, is a contraindication to treatment with arsenic in any but small doses

It seems probable that the arsenic compounds may tend to aggravate or accentuate a cirrhotic process in hepatic disease Therefore, liver disease and jaundice are contraindications to arsenic therapy

Febrile illnesses, acute infections such as colds, pneumonia, typhoid fever, etc., contraindicate the use of arsenical compounds for the time being Such infections may increase the risk of severe untoward arsenic reactions

Malnutrition and cachexia seem to be attended by more severe reactions than occur in well-nourished persons Recently it has been shown that vitamin C may have a detoxifying action with respect to arsenic This may be shown to have a practical application in reactions to treatment

Chronic skin diseases contraindicate the use of arsenic, for it is generally

accepted that their presence increases the tendency toward the cutaneous reactions to arsenic. Exfoliative dermatitis definitely contraindicates the further or subsequent use of a trivalent arsenical preparation. Tryparsamide may be used in such cases for the treatment of neurosyphilis if present.

Optic nerve involvement due to syphilitic or other cause contraindicates the use of tryparsamide.

#### UNTOWARD REACTIONS TO ARSENICALS

**Trivalent Arsenicals** This discussion will be mainly concerned with those of systemic nature. A few local reactions will be mentioned briefly.

**LOCAL REACTIONS** Pain radiating along the vein may be experienced at the time of injection. This occurs especially in the use of over alkalinized arsphenamine. Of the arsenic preparations administered by syringe, however, this complaint is practically only associated with mapharsen. Its frequency with this drug can be reduced only by the rapid injection of the solution. Thrombosis of veins occurs in the use of over alkalinized old arsphenamine.

The most serious local reaction is that due to infiltration of the tissues about the vein by an arsenical solution. At the time of injection the patient becomes aware of a burning sensation at the site of injection. The physician should note local swelling of the tissues or increased resistance to injection. If the solution is injected in quantity the pain is intense, lasts for some days, and in some cases the arm cannot be used for several weeks. The swelling is tender and presents redness of the overlying skin. At times a firm nodule persists for weeks. A slough may occur laying bare the deeper tissues of the arm and may heal with a scar causing contracture. Infiltrations with mapharsen seem to be much more benign than those occurring with the arsphenamines. Prevention is the best treatment. Complaint of pain by the patient is indication for withdrawal of the needle. If infiltration has occurred, the injection of some normal saline either alone or with novocaine dilutes the arsenic solution and seems to reduce the possibility of sloughing. Hot applications, analgesics and sedatives, and a sling for the arm provide the best symptomatic treatment.

**CONSTITUTIONAL REACTIONS** are varied, with symptoms and signs which are general or related to systems such as the gastro intestinal tract, liver, skin, blood forming organs, and brain. Death occurs occasionally as the result of certain of these reactions, but has become less frequent with the passage of time. In the early years of arsphenamine therapy 1 death per 3,777 injections was reported, in late years this has dropped to about 1 per 33,000 injections. The frequency of the systemic reactions is shown in the following table published by the Co-operative Clinical Group, and re

presenting 177,360 injections of an arsenical drug I have adapted material from two of the original tables to show the frequency of the various treatment reactions as they occurred with the use of arsphenamine and neoarsphenamine only. The frequency is related only to patients treated or observed for six months or more and is expressed in total reactions and injections, and in the rate of reactions per 1,000 injections. Information relative to some of the items included in Table IV is not very definite, but in general this list gives some idea of the frequency and variety of the complications of arsenic therapy.

In contrast to the arsphenamines, the use of arsenoxide is accompanied by relatively few reactions, and these generally of no severe consequence. Gruhzt and his collaborators reported on 75,589 injections of this drug given to 4,841 patients. They encountered no severe reactions and no deaths. Gastro-intestinal reactions, some of moderate severity, occurred in 4.4 per 1,000 injections. Other authors have reported as high as 14 per cent of gastro-intestinal reactions. Jordan and Traenkle reported upon 110 patients who had had untoward reactions to arsphenamines and who were subsequently treated with mapharsen. Those with gastro-intestinal reactions took the latter well. Mapharsen caused no nitritoid reactions in twenty who had had severe ones before. Sixteen of eighteen patients who had had arsphenamine jaundice did well with mapharsen. Five with mild dermatitis had no recurrence with the use of mapharsen. One patient who had had a previous exfoliative dermatitis had a recurrence after mapharsen therapy. During 1939, the experience in the U S Navy was that there was a threefold incidence of reactions with the use of neoarsphenamine over that with mapharsen.

The cause of certain of the constitutional reactions to the injection of arsenicals is not known. Several factors may be involved in the possible explanation of such untoward effects, as (1) the mere mechanical effect of injecting a foreign substance intravenously, (2) the fact that the solution is colloidal, and (3) the toxic effect of the drug itself.

One may also look upon reactions as being early, related to the mechanical effect of the injection, and as late, due to the chemical nature of the drug. Among the early reactions are several which are worthy of mention.

**GASTRO INTESTINAL REACTIONS** It is obvious from Table IV, and every clinician's experience, that gastro intestinal reactions are the most frequent, occurring with varying frequency with all the trivalent arsenical preparations. Usually nausea or vomiting occurs very shortly after the injection of the drug, although sometimes these symptoms are delayed for some hours. Diarrhea likewise may occur. Avoidance of food in quantity for several hours before and after the injection may prevent these symptoms. Control of constipation by mild laxatives may be effective in the

TABLE IV

FREQUENCY OF EACH TYPE OF TREATMENT REACTION OCCURRING AMONG THE TOTAL INJECTIONS OF EACH ARSENICAL ADMINISTERED TO THE TOTAL NUMBER OF PATIENTS TREATED OR OBSERVED FOR SIX MONTHS OR MORE\*

<i>Reactions to Treatment</i>	<i>Treatment Reactions to the Arsenical Drug</i>			
	<i>Total</i>		<i>Rate per 1,000 Injections</i>	
	<i>Old Arsphen amine</i>	<i>Neo-arsphen amine</i>	<i>Old Arsphen amine</i>	<i>Neo-arsphen-amine</i>
<b>Mild</b>				
Gastro-intestinal reaction	537	205	5.07	6.66
Nitritoid reaction	542	75	5.12	2.44
Pruritus	102	48	.96	1.56
Slight skin eruptions	263	87	2.48	2.82
Transient kidney irritability	117	7	1.10	.23
Total mild	1,561	422	14.73	13.71
<b>Severe</b>				
Acute yellow atrophy of the liver	2	0	.02	—
Aplastic anaemia	0	3	—	.10
Arsenical stomatitis	3	3	.03	.10
Crustaceous dermatitis	96	25	.90	.81
Icterus	123	37	1.16	1.20
Ocular damage	0	0	—	—
Purpura hemorrhagica	4	5	.04	.16
Venous embolus	0	1	—	.03
Death	2	1	.02	.03
Total severe	230	75	2.17	2.43
Total reactions	1,791	497	16.90	16.14
Total injections	105,942	30,779		

\* From Ven. Dis. Inform.

prevention of the intestinal symptoms. Generally it is not necessary to discontinue or radically to alter treatment. However, if gastro intestinal symptoms are severe, lasting twenty-four hours or more, reduction in dosage may be necessary. The dangers of inadequate dosage in acute syphilis will be emphasized in Chapter VIII, and therefore it is probably better to try other trivalent arsenical compounds instead of reducing the

**dosage** At times one finds patients who cannot take any arsenical drug without severe gastro intestinal symptoms. As a word of warning it must be emphasized that severe gastro-intestinal reactions, sometimes lasting for several days, may presage serious reactions such as exfoliative dermatitis.

**HEADACHE AND CHILLS** also are early reactions which may come on a few hours after the injection of an arsenical preparation other than tryparsamide. These generally are of little significance if they are of mild degree. Severe or recurrent chills often antedate serious dermatitis.

**NITRITOID REACTION** The outstanding reaction of the early type is the nitritoid ("anaphylactoid" or "angioneurotic syndrome") reaction. The symptoms are probably mainly vaso motor in origin and due to the mechanical effect of the injection of a colloidal solution ("speed shock"). Certainly one may see the identical reaction associated with the injection of solutions other than an arsenical one. The nitritoid reaction occurs either during or immediately after the injection of an arsphenamine. There is flushing of the face, and injection of the conjunctiva. The patient complains of burning of the tongue and throat, palpitation, dyspnea, and choking. A sense of oppression in the chest may occur with coughing or vomiting. Often there is pain commonly referred to the chest, lumbar muscles, and thighs. The pulse is weak, and the blood pressure may drop. Syncope may occur. There may be swelling of the eyelids, face, lips, tongue, and vocal cords. Urticaria is not uncommon. If the symptoms begin during the injection, stopping it may abort the attack. At most the symptoms last from ten to thirty minutes without treatment. Epinephrine hypodermically usually relieves the nitritoid attack promptly. Although the reaction may be alarming to the patient, and to the inexperienced physician, there is little to fear in it. It does not follow that a nitritoid reaction will appear after each succeeding injection of a given drug because it has occurred after the use of that drug on a previous occasion. The slow injection of the arsenic preparations may eliminate the nitritoid attack. If recurrences are persistent a change of drug is advisable. Arsenoxide is rarely associated with such reactions, and therefore is a good drug to use as an alternate to the arsphenamines in patients subject to nitritoid reactions. We have found it feasible to prevent recurrent attacks by the preliminary oral use of ephedrine sulphate gr  $\frac{1}{2}$ , twenty to thirty minutes before the injection, or by the subcutaneous injection of epinephrine, 3 minims a few moments before the injection.

**MEDICAL SHOCK** is a rare reaction which has been described a few times. In this state there is circulatory collapse, not responding to epinephrine, and probably representing a capillary paralysis. All the findings attendant upon surgical shock are present. Treatment consists of the injection of fluids, especially plasma.

There are several types of late reactions to the injection of trivalent arsenic. The use of arsenoxide has been associated with practically no examples of these reactions. No adequate explanation has been advanced to date to account for the untoward effects of organic arsenic in producing the late-treatment reactions. Sensitization to the drugs has been thought to account for some reactions, but the explanation is not so simple.

**DERMATITIS** The following types of dermatitis may occur.

*Urticaria* has been mentioned above under the heading of the nitritoid reaction. It usually makes its appearance fairly soon after the injection, at most in a day or so, is evanescent, and is usually controlled by the use of epinephrine. It may appear after one or more injections of an arsenical preparation. A change to another form of arsenic is usually successful in eliminating this type of dermatitis. (See Case 43.)

*Pruritus* without urticaria or other visible changes in the skin may occur after arsenic therapy. In the absence of urticaria it should not be passed over too lightly for it may be the forerunner of exfoliative dermatitis.

*Exanthematous rashes* are most commonly seen during the first course of arsenical therapy. These are sometimes classified as the "ninth-day erythema." This name has been applied because it often comes on after the second or third injection of a trivalent arsenical drug on the eighth or ninth day. Some twelve to forty-eight hours after the injection the patient develops a mild temperature elevation, gastro-intestinal symptoms, and generalized aching of muscles and joints. This will be followed by an exanthematous rash, especially on the trunk and extremities. The rash may be erythematous or scarlatiniform, it may be macular or morbilliform. Edema of the eyelids occurs. Such rashes last for several days, and then fade, at times with a fine desquamation. In these cases arsenic should be given with care subsequently. In general, after a period of several weeks, a trial may be made with a small dose of the same drug, or preferably with another. With arsenoxide now available, this should be the drug of choice in a patient who has had an exanthematous rash. As a test it should be used in a dosage of 0.01-0.015 Gm., and if there is no recurrence of the rash the dosage may be increased.

*Papular eruption* is more serious. Within twenty-four to forty-eight hours after the injection of arsenic, a papular infiltration of the skin occurs. This is most likely to involve the flexor surfaces of the elbow, axillae, neck, groins, and popliteal spaces. It often becomes more diffuse in its infiltration of the skin, and may assume a papulovesicular nature. Fissures of the skin and vesicles appear so that the surface presents a weeping eczematoid state. Constitutional reactions—fever, chills, etc.—are associated with it. The mild papular lesions may show little scaling, whereas papulovesicular types do show some exfoliation. This form of dermatitis is probably the

mildest form of exfoliative dermatitis (See Case 5) *The further use of trivalent arsenic is not to be considered* Tryparsamide may be used subsequently if central nervous system syphilis is present

**Case 5** A seventeen year old married woman had been found to be sero positive during her first pregnancy two years before. At that time she received fifteen intravenous and sixteen intramuscular injections, and five of each post



FIG 3 Arspenamine dermatitis—papular (Case 5)

partum. Upon her first visit to the Syphilis Clinic she was three months pregnant, and presented positive blood Wassermann and Kahn tests. She was given arspenamine 0.3 Gm  $\times$  5,\* neoarsphenamine 0.45 Gm  $\times$  5, and bismuth  $\times$  2. She developed bronchopneumonia and was delivered of a premature child which died on the sixteenth day of life.

Treatment was continued: the patient receiving arspenamine 0.3 Gm  $\times$  5, neoarsphenamine 0.45 Gm  $\times$  9, and bismuth  $\times$  13. She became pregnant again. During neoarsphenamine therapy itching developed, and in a few days the skin in the axillae, antecubital and popliteal fossae became red and indurated. Mild changes occurred in the skin about the neck. Slight exfoliation occurred. Papules bordered the indurated areas.

**Comment** This is an illustration of arsenical dermatitis which was at first papular, then became more indurated with a very mild exfoliation. Dosage had never been excessive for the patient's weight was 120 lb. She did not tolerate arsenicals well, as a change from arspenamine was necessary in both courses because of nausea and vomiting. Figure 3 shows papules at the borders of the more extensive indurated lesions in the axillae. Noteworthy is the great amount of arsenic the patient received before dermatitis appeared.

\* In the case reports  $\times$  followed by a number will designate the number of injections given.



*Exfoliative dermatitis* is the most serious form of skin reaction to arsenotherapy, and may end fatally. At times the onset may be sudden, again it may be preceded by itching and fever following several preceding injections of arsenic. A history of severe and persistent gastro-intestinal reactions following the preceding treatments may be obtained. Within twenty-four to forty-eight hours after the injection which is followed by the attack of exfoliative dermatitis, erythema appears, usually quite generalized. Here and there are patches of infiltration, especially at the flexures, as was described in the papular dermatitis, of which some are dry and some are wet. Itching is intense, and chills and fever occur, the latter often reaching 103° F or so. Renal irritation may occur, indicated by albuminuria, casts, and red cells. The indurated, red, weeping skin gradually becomes drier, brown, and thickened. Extensive scaling occurs, with at times large areas of exfoliation (palms and soles). The hair and nails may be lost. Secondary skin infection occurs, manifested as furuncles, subcutaneous abscesses, and bedsores. These septic foci may be the source of a septicemia and death. A general lymphadenitis is the rule, and glands may suppurate and require surgical drainage. The exfoliative process may also involve the conjunctiva and the mucous membranes of the mouth. The process may also involve the mucosa of the bronchioles, leading to their obstruction, bronchopneumonia, and death. Eosinophilia may occur. The duration of the skin disease is, in severe cases, six to ten weeks. After recovery from exfoliative dermatitis, the skin is hypersensitive, and may show mild exfoliation as the result of exposure to sunlight. Drugs other than arsenic, including bismuth, if given too soon, may cause a slight recurrence. *A patient who has had exfoliative dermatitis must never receive another injection of trivalent arsenic, no matter how small.* Tryparsamide may be used, however, in the treatment of neurosyphilis. Case 6 is an example of exfoliative dermatitis.

**Case 6.** A twenty-nine year-old, white divorcee entered the Medical Clinic because of a rash. About four months before she developed genital lesions and was found to be seropositive. Three months before admission she received three intravenous injections at four-day intervals. The last of these caused headache, nausea, and vomiting. Bismuth was then given for three weeks.

Five weeks before admission she was given one intravenous injection which was followed in twelve hours by malaise and nausea. A week later she developed a "pimply rash" in the folds of her skin, which itched intensely, and spread to involve the whole body. It reached this extent two weeks before admission, and one week before, the face, ankles, and feet became swollen. Four days before admission scaling began with "wet" areas. There was chilliness, dyspnea, and discharge from the ears.

**EXAMINATION.** The skin was red, infiltrated, and covered with scales. Fissures, weeping a serosanguineous fluid, were present at the angles of the eyes.

and mouth, in the axillae, antecubital and popliteal fossae, and inguinal regions. The external auditory canals were filled with pus. The nares were filled with crusts. The mucosa was desquamating over the hard palate. There was a large generalized lymphadenopathy. Pustules were scattered over the body. The legs were edematous. The temperature ranged from 99-104° F for three weeks and then dropped to 99-100° F for another two weeks. There was slight anaemia. Blood tests for syphilis were negative. Serum proteins were low. The urine was negative. The white-blood-cell count was 14,000-17,000 per cu mm, with an eosinophilia of 15-30 per cent. Polymorphonuclear cells were 60 per cent. Hemolytic staphylococcus was grown from the pustules and from the blood stream. One abscess was drained in each axilla and in the left groin.

The patient received four blood transfusions. The bacteremia was treated with one of the sulfonamide drugs. The patient was discharged from the hospital five weeks after admission, greatly improved.

**Comment.** This patient presented the classic picture of a severe exfoliative dermatitis due to arsphenamines. The constitutional manifestations, the cutaneous lesions and the various laboratory findings were typical. Furunculosis and subcutaneous abscesses such as occurred in this patient are not uncommon. In this patient the blood culture was positive more than once for a hemolytic staphylococcus. Blood stream infection is one cause of death in patients having exfoliative dermatitis. In this case, it is probable that the use of sulfonamide drugs saved the patient's life (Figure 4).

The cases of arsphenamine dermatitis seen at the Vanderbilt University Hospital were reviewed by Jones. During the decade 1927-37, thirty-two occurred. Of these fifteen represented full-blown exfoliative dermatitis, the remainder were less severe. Females developed severe dermatitis twice as frequently as did males, twenty-one of the thirty-two cases occurring in women. Rather marked gastro-intestinal reactions had occurred in twelve of the thirty-two cases before the onset of dermatitis. The frequency of severe dermatitis in our clinic during that decade was 1 case per 1,877 injections of an arsphenamine. However, in other years it has varied from 1 per 888 to 1 per 8,050 injections. Even when allowance is made for the frequency of its use, neoarsphenamine therapy was found to be attended by the highest incidence of severe dermatitis. Severe dermatitis accompanied the use of the arsphenamines as follows:

Neoarsphenamine	17 cases
Arsphenamine	9 cases
Arsphenamine and neoarsphenamine	3 cases
Sulfarsphenamine	1 case
Sulfarsphenamine and neoarsphenamine	1 case
Stovarsol	1 case

In the Vanderbilt University Hospital patients, severe dermatitis appeared

in 75 per cent before the ninth injection of an arsphenamine. One occurred after the eighteenth injection. In one case in which one injection of neoarsphenamine was given as a provocative test, the first symptoms of exfoliative dermatitis appeared the next day.

Some authors report a high mortality in exfoliative dermatitis. At

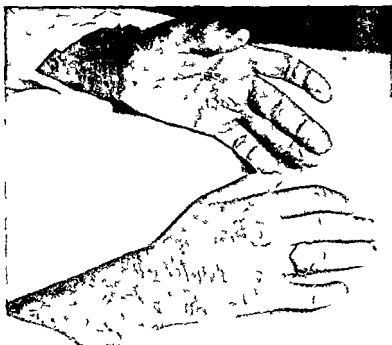


FIG 4 Arsphenamine dermatitis—exfoliative (Case 6)

Vanderbilt University Hospital, Jones found only one death among the fifteen patients who had it.

The treatment of exfoliative dermatitis is symptomatic. All antisypilitic treatment must be stopped at once. Consultation with a dermatologist may be advisable. Treatment can be best carried out in a hospital. The use of colloidal baths, and the application of olive oil to the skin, give most symptomatic relief. Suppurative areas should be drained surgically. Sodium thiosulfate intravenously and by mouth in the treatment of exfoliative dermatitis was much in vogue about two decades ago, but its value was never definitely established. Very recently the subject has again been reopened by reports that large doses of this chemical shortens the course of the disease and makes it milder.

*“Fixed” Arsphenamine Dermatitis and Herpes Zoster.* Less frequent than the above skin lesions are “fixed” arsphenamine dermatitis and herpes

zoster In the former condition localized patches of cutaneous induration occur They may be either eczematoid or pigmented These are uncommon, and may disappear between injections or partially subside between injections Herpes zoster has appeared uncommonly in our patients, and has involved a variety of nerve distributions It is questionable whether this skin lesion is directly related to arsenic therapy In our experience it has never recurred after the subsequent use of arsphenamines, and we feel certain that the incidence of herpes zoster is as great among the patients in the Medical Clinic as in the Syphilis Clinic

In summary, it should be emphasized that severe gastro intestinal reactions may point to the subsequent development of dermatitis In the presence of itching, arsenic should be withheld for one or two injections in order to see what will develop With skin symptoms and mild dermatitis it is wise to stop the arsphenamine in use, and to employ mapharsen subsequently to avoid possible serious reactions A fair proportion of the cases of exfoliative dermatitis brought into Vanderbilt University Hospital have given a history of symptoms and signs that should have been a danger signal for the attending physician In case of doubt it is best to stop the use of arsenic and await results The presence of a nonarsphenamine dermatitis may predispose to the development of arsenical dermatitis

TABLE V

THE NUMBER OF INJECTIONS OF ARSENIC AND ITS TYPE BEFORE THE APPEARANCES OF ICTERUS (VANDERBILT UNIVERSITY HOSPITAL CASES)

<i>Number of Injections</i>	<i>Number of Cases</i>
Old arsphenamine	
1 10	12
11 20	1
Neorsphenamine	
1 10	4
11 20	5
21-40	2
Old arsphenamine and neorsphenamine	
1-10	4
11-20	3
21-40	2
Neorsphenamine and mapharsen	
1-10	1
11-20	2
	—
Total	36

JAUNDICE Next to dermatitis jaundice is the most frequent of the more severe reactions to arsenic Though organic arsenic preparations are

known to produce liver necrosis in the experimental animal, several authors have raised the question as to whether the drug is the only factor in the production of jaundice in man. Intercurrent infection as a possible factor has been considered by some authors. We have felt that in some instances the condition was acute catarrhal jaundice rather than arsenical hepatitis because of a similar condition in the patient's associates or in the population at large. It is very possible that arsphenamine is only one factor. Even in acute yellow atrophy—fortunately the rare though often fatal form of hepatic disease—there may be other factors. In several patients who have died in Vanderbilt University Hospital, pregnancy has been a factor in addition to arsenic therapy. Both are known to cause liver necrosis at times.

It must not be forgotten that syphilitic hepatitis may be the cause of jaundice. Acute syphilitic hepatitis with jaundice may occur in the secondary stage of syphilis or as a hepato-recurrence. Furthermore, jaundice appearing early in syphilis, upon the institution of treatment, may be indicative of a Herxheimer reaction.

Arsphenamine icterus may appear early in treatment, or late in treatment, after repeated courses of arsenic. Table V shows the total number of injections of arsenic before hepatitis occurred. Since most of these patients were on continuous treatment consisting of alternating courses of heavy metal and arsenic, the approximate time at which jaundice appeared during treatment may be estimated.

The time relationship of the appearance of jaundice to the last injection of arsenic in the thirty-six cases in our clinic is shown in Table VI.

TABLE VI

DAYS ELAPSED BETWEEN THE LAST INJECTION OF ARSENIC AND THE  
APPEARANCE OF ICTERUS

<i>Number of Days Since Last Injection</i>	<i>Number of Cases</i>
1-14 inclusive	18
15-30 inclusive	7
31-90 inclusive	9
91 days or more	1
Heavy metal only	1
Total	36

Of these thirty-six cases shown in Table VI, jaundice appeared during a course of heavy metal in eight. In three instances icterus appeared after the use of mapharsen. A change had been made to this drug because of reactions to other arsenical compounds.

The clinical picture of arsenical hepatitis varies from a mild asymptomatic jaundice to acute yellow atrophy and death. Usually, the clinical course is like that of acute catarrhal jaundice from which it is indistinguishable except in that the patient has had arsenical therapy. Malaise and generalized aching, anorexia, nausea, vomiting, and low-grade fever constitute the symptomatology. The liver is palpable and tender. There may be splenomegaly. Jaundice is present, bile appears in the urine, and the stools are acholic. Rarely the condition goes on to acute yellow atrophy, and death results from hepatic insufficiency. The duration of the disease varies from days to several weeks or longer. In the past much speculation has been given to possible residual liver damage. Rankin and Marlow recently studied the subsequent course in sixty-two cases of postarsphenamine jaundice. No cirrhosis was demonstrated in uncomplicated cases. Evidence of mild impairment of hepatic function was demonstrable in cases in which liver damage had been severe or in those instances in which the patients also were addicted to the use of alcohol.

The management of the patient with arsphenamine hepatitis is similar to that of acute catarrhal jaundice. Antisyphilitic treatment is stopped at once. The question of the use of arsenic in subsequent antisyphilitic treatment will arise. It is the experience of various authors as well as our own that recurrent attacks of jaundice are not seen. Arsenic therapy was used in twenty-four of our thirty-six cases of so-called arsphenamine jaundice after some interval, following the disappearance of icterus, without any recurrence. In some of these, frequent check by icterus-index determinations during subsequent treatment with arsenic revealed no evidence of bile-pigment retention. The factors which will determine the subsequent use of arsenic therapy are several.

If the jaundice has been associated with a stormy course suggesting subacute yellow atrophy, or if impairment of hepatic function persists, as determined by function tests, or if the patient is an alcoholic, the further use of arsenic is to be avoided. If jaundice appears in the last course of arsenic treatment planned for the patient, the subsequent use of the drug is hardly worth while. However, given a patient with early syphilis who has received inadequate amounts of an arsenical drug and with the jaundice of the average severity and duration, one's attitude may reasonably be different. Here, in weighing probabilities, the lesser of two evils is the subsequent use of arsenic. The antisyphilitic treatment in such a case in our hands is somewhat as follows. Icterus-index determinations are made weekly. After normal values have been established, treatment with bismuth is begun, accompanied by iodides. This is continued for about eight weeks. Then a small dose of an arsenical compound, preferably arsenoxide, is given. The icterus index is determined some days later. The doses of

known to produce liver necrosis in the experimental animal, several authors have raised the question as to whether the drug is the only factor in the production of jaundice in man. Intercurrent infection as a possible factor has been considered by some authors. We have felt that in some instances the condition was acute catarrhal jaundice rather than arsenical hepatitis because of a similar condition in the patient's associates or in the population at large. It is very possible that arsphenamine is only one factor. Even in acute yellow atrophy—fortunately the rare though often fatal form of hepatic disease—there may be other factors. In several patients who have died in Vanderbilt University Hospital, pregnancy has been a factor in addition to arsenic therapy. Both are known to cause liver necrosis at times.

It must not be forgotten that syphilitic hepatitis may be the cause of jaundice. Acute syphilitic hepatitis with jaundice may occur in the secondary stage of syphilis or as a hepato recurrence. Furthermore, jaundice appearing early in syphilis, upon the institution of treatment, may be indicative of a Herxheimer reaction.

Arsphenamine icterus may appear early in treatment, or late in treatment, after repeated courses of arsenic. Table V shows the total number of injections of arsenic before hepatitis occurred. Since most of these patients were on continuous treatment consisting of alternating courses of heavy metal and arsenic, the approximate time at which jaundice appeared during treatment may be estimated.

The time relationship of the appearance of jaundice to the last injection of arsenic in the thirty-six cases in our clinic is shown in Table VI.

TABLE VI

DAYS ELAPSED BETWEEN THE LAST INJECTION OF ARSENIC AND THE  
APPEARANCE OF ICTERUS

<i>Number of Days Since Last Injection</i>	<i>Number of Cases</i>
1-14 inclusive	18
15-30 inclusive	7
31-90 inclusive	9
91 days or more	1
Heavy metal only	1
Total	36

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arsenic are gradually increased, checked by icterus-index determinations and eventually treatment, as originally planned, is resumed

**DEPRESSED BONE-MARROW FUNCTION** Fortunately, this is a rare complication of the use of the arsphenamines. The organic arsenical drugs as a group are only one of a number of substances known to be toxic at times to the bone marrow. Thus there is nothing characteristic of these blood dyscrasias when due to arsenic intoxication. Sulfarsphenamine has been the commonest offender. These reactions have not been reported with the use of arsenoxide. The subsequent use of trivalent arsenic is not to be considered.

**THROMBOCYTOPENIA** with its manifestations of purpura is due to interference with the production of blood platelets. The manifestations of purpura familiar to every physician are those of bleeding from the mucous membranes, and petechial or larger hemorrhages into the skin. It makes its appearance in eight to fourteen days after an injection of arsenic. Recovery is the rule. Transfusions may be necessary.

**GRANULOCYTOPENIA**, or agranulocytosis, is an expression of damage to the polymorphonuclear-leukocyte-producing mechanism. As new leukocytes fail to form, the blood smear will contain only the more mature cells. The white-cell count drops steadily, until finally the total count may be only a thousand or so cells, and then mainly lymphocytes. The clinical picture may be that of agranulocytic angina, or that of an overwhelming infection. In the former, necrotic ulcers may form in the oral or pharyngeal cavities, or in the vagina. (Before agranulocytosis was recognized as such, this condition was known as arsenical stomatitis.) Transfusions may tide the patient over the period of depression of white-blood-cell production until the normal state is again present.

Two cases of this complication have occurred in our clinic—one after arsphenamine, and one after sulfarsphenamine. In the first an upper respiratory infection was present at the time of the one injection of the drug, and was probably a predisposing factor. The other patient developed symptoms after the third injection. Both patients presented lesions of the throat and tonsils, and had high fever. The white blood counts were three to four thousand in each case with 3.5 and 4 per cent of polymorphonuclear cells. Recovery occurred in each case. One patient was treated some years later with mapharsen during a pregnancy without further trouble.

**APLASTIC ANAEMIA** results from damage to the red blood-cell-producing mechanism, and is practically always fatal. Associated with it are the other two aspects of bone-marrow depression. There is a steady decline in the red-blood-cell count without the appearance of young cells in the circulation. Repeated transfusions are worthy of trial in the hope that

erythropoiesis will be re-established. The only patient who has been admitted to Vanderbilt University Hospital with the diagnosis of aplastic anaemia due to arsphenamines was one who had been receiving neoarsphenamine. Upon admission his blood showed a count of 920,000 red cells and a hemoglobin of 2.2 Gm. He died in spite of ten transfusions.

In the last few years a form of *purpura* has been described, seemingly due to sensitivity to the arsphenamines. (Most of these cases have received neoarsphenamine.) This uncommon condition is apparently due to a rapid decrease in the circulating blood platelets. In the usual form of *purpura* the manifestations first appear at about eight to fourteen days, when the lack of platelet formation is felt. In this recently recognized condition the effect is immediate in that symptoms appear within minutes, or at the most some hours, after the injection. A rapid fall in circulating platelets can be demonstrated within thirty minutes after administration of the drug. Petechiae soon appear on the mucous membranes or in the skin. In one of our four cases the platelets disappeared completely, and bleeding from the gums was profuse, all bleeding stopped in seventy-two hours, and platelets again rose to normal levels. In our cases, as in the few reported in the literature, this type of reaction occurred following the use of an arsphenamine. Arsenoxide apparently has no effect upon the circulating platelets, and may be used with impunity for subsequent treatment in these cases. Transfusion will stop the bleeding at once. (See Cases 89 and 98.)

HAEMORRHAGIC ENCEPHALITIS is the rarest of the complications of arsenic therapy. It has occurred with the arsphenamines given intravenously, and with sulfarsphenamine given intramuscularly. Recently, several instances have been reported due to "massive-dose therapy" with mapharsen. The frequency of pregnancy in the reported cases has been high. Death occurs in practically all cases. Several of the patients treated by "massive-dose therapy" with mapharsen have had periods of unconsciousness indicating possibly a milder degree of haemorrhagic encephalitis. Recovery has been complete in these. At autopsy section of the brain shows the cut surface to be studded with multiple petechial haemorrhages. Microscopically, the capillary walls are found to be broken.

The manifestations begin to appear two or three days after an injection of an arsenical compound. Headache, dizziness, and vomiting occur. Mental excitement followed by delirium, convulsions, and coma appear in rapid succession, and death usually occurs several days after the onset of symptoms.

Two of the three cases of haemorrhagic encephalitis admitted to Vanderbilt University Hospital have occurred in women, one of whom was pregnant and did not have syphilis. She had received 0.3 Gm. of neo-

arsphenamine. The other was a woman in whom two doses of 0.3 Gm neoarsphenamine had been used as a provocative test. The third patient was a male who had primary syphilis. The complication developed after the seventh injection of neoarsphenamine. In all three cases the onset of symptoms was from three to five days after the last injection of arsenic. Death occurred on the fourth or fifth day in each case. Necropsy in two cases showed the characteristic pathologic findings in the brain.

**NEPHRITIS** due to the arsenical drugs is rare, and generally of little importance by itself. Renal irritation may be part of the picture of exfoliative dermatitis or haemorrhagic encephalitis.

**PERIPHERAL NEURITIS** due to the use of the arsphenamines is rare, but has been reported after long courses of arsenic. Neoarsphenamine was used in the first series of patients treated by the "intravenous drip method," and a high percentage of the patients developed this complication. The change to mapharsen in this experimental form of treatment has eliminated this particular reaction.

**Pentavalent Arsenicals.** Reactions to tryparsamide are few, and with one exception not alarming. Mild gastro-intestinal reactions occasionally occur. Jaundice has been reported, but because of its rarity may represent coincidence. Nitritoid reactions may occur. Dermatitis is rare, and, when it occurs, mild. Only about thirty cases of dermatitis due to tryparsamide have been reported in the literature. This pentavalent arsenical compound may be given to patients who have had exfoliative dermatitis. Occasionally mild desquamation may occur in patients who have had previous exfoliative dermatitis due to trivalent arsenicals, but no fatalities have ever been reported.

**OPTIC ATROPHY** is the untoward effect of tryparsamide therapy which is to be feared. In her exhaustive review of the literature on tryparsamide, Hinrichsen found that several authors reported that about 20 per cent of patients under treatment with the drug complained of visual symptoms. Though most of the ocular reactions occur in the first course of tryparsamide, this is not always true. Subjective complaints come on within a day or so of treatment, and our patients almost always voluntarily describe the distorted visual images as in "heat rising from the pavement." Vision may be so impaired that the patient is almost blind, as occurred in Case 7, but some degree of recovery is the rule. Visual-field studies show that there is almost always some residual constriction of the fields. In most patients with subjective symptoms, examination will reveal little. However, the disks may be hyperemic. Pallor of the disks may become obvious with the passage of months.

**Case 7.** A forty-four-year-old Negro was first admitted to the Medical Clinic. There was no history of acute syphilis.

The physical examination was negative. Blood Wassermann and Kahn tests were positive. Spinal fluid study showed a trace of globulin, 2 cells per cu mm., the Wassermann test was positive in 1, 0.5, 0.2 cc dilutions, and the mastic curve was flat. Arsphenamine 0.4 Gm.  $\times$  11, and bismuth  $\times$  14 were given, after which treatment was lapsed.

He was next seen four years later because of complaints unrelated to syphilis.

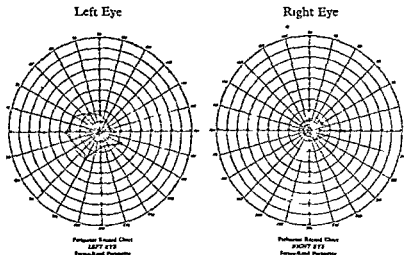


FIG. 5 Tryparsamide amblyopia (Case 7)

Blood Wassermann and Kahn tests were negative. Spinal fluid examination showed no globulin or cells, a positive Wassermann test in 1 and 0.5 cc. with a negative mastic test. In the next seventeen months the patient received neoarsphenamine 0.6 Gm.  $\times$  21, and bismuth  $\times$  21. The spinal fluid showed no change at the end of this time. Therefore, in the following sixteen months he received tryparsamide 3 Gm.  $\times$  26, and bismuth  $\times$  27. At the end of this time the spinal fluid was negative in all respects.

Examination by the ophthalmologist before the drug was begun was negative. After each injection of tryparsamide the patient was questioned relative to untoward effects. Following the twenty-fifth injection he noted "flashes of light" for two days after injection, but failed to mention this to us. The same symptoms recurred the day after the twenty-sixth injection. His vision then became dimmer, so that five days later when we saw him he said he was almost blind. Examination by the ophthalmologist showed the vision as follows: O.D. 0, O.S. 10/50. A week later vision was O.D. 20/50, O.S. 20/40. There was marked constriction of the visual fields at this time (Figure 5). The optic disks were pale. Thirty days after the last injection of tryparsamide, the patient said his vision was as good as it had ever been. Several times subsequently vision was found to be 20/30 in both eyes.

**Comment.** Toxic amblyopia due to tryparsamide appeared after twenty-six injections of the drug. This case demonstrates the amount of recovery possible from even a high degree of visual impairment.

Disease of the optic nerves, as in *tabes dorsalis*, constitutes a contraindication to the use of tryparsamide. In the presence of such disease the remaining vision may be blotted out by the use of the drug. The avoidance of untoward effects from the use of tryparsamide requires that the physician must be sure that no disease of the optic tract is present. Under treatment, visual complaints necessitate discontinuance of the drug, and a check-up examination by the ophthalmologist.

#### SUBDURAL THERAPY

The intraspinous (Swift-Ellis treatment) use of arsphenamine is occasionally indicated in neurosyphilis. It is of no value in paresis, and is used only under certain circumstances in *tabes dorsalis*. The conditions for its use will be indicated in the chapter on neurosyphilis. The details of the technic will be omitted because it should be used only in the hospital, and has no place in the hands of the average physician. As will be indicated later, certain phases of neurosyphilis require consultation with a neurologist or internist interested in the field of syphilis. Such a consultant should be the one to supervise intraspinous therapy.

Briefly, this method of treatment is somewhat as follows. About twenty minutes after the intravenous injection of a full dose of an arsphenamine, blood is drawn by venipuncture. Upon standing the clot will have separated by the next day. The serum then is centrifuged, and heat-treated. By spinal or cisternal puncture 10-15 cc. of spinal fluid are removed, and about 10 cc. of the patient's arsphenaminized serum is permitted to run in by gravity. Such treatment is given once in two weeks with six to eight treatments per series. Arsphenamines are given intravenously in the intervening weeks.

Severe pain and sphincter disturbances may follow such treatment. At times *transverse myelitis with paraplegia*, which may be permanent, may occur. Such dangerous complications seem to appear more often with intraspinous treatment at the lumbar region, than with intracisternal injections (Moore).

#### "MASSIVE-DOSE THERAPY"

Before leaving the subject of arsenic therapy in the treatment of syphilis, passing mention must be made with reference to the "five-day treatment," "intravenous-drip treatment" or "massive-dose therapy." This experimental study is one of the most interesting schemes that has been offered in the treatment of syphilis in recent years. Its objective is to provide a rapid method of treatment applicable to early syphilis. If successful, such a scheme would permit "cure" in such a short period of time as to eliminate the almost universal tendency to abandon treatment when it is prolonged.

If acute cases of syphilis could be isolated and "cured" in five days, the millennium of syphilis control would be here

Because of its relative nontoxicity, mapharsen has been the drug of choice, and large doses may be given by an intravenous drip. Untoward reactions have occurred, infectious relapses have appeared. This method is obviously experimental, requires the hospitalization of patients, the attendance of a trained personnel, and will require a number of years of follow-up study in order that results may be evaluated. *Therefore this treatment method is not for use by the average practitioner.* Until the worth of this experiment has been proved, and until the method has been made practical for use in the field, the physician engaged in treating syphilis must use older and proved methods.

It seems possible that out of this experimental therapy there may evolve some plan of multiple doses at frequent intervals, thereby shortening the course of antisyphilitic treatment.

## THE HEAVY METALS

The two heavy metals of use in the treatment of syphilis are bismuth and mercury. The latter, of interest from a historical viewpoint, now has assumed a secondary place to bismuth, which has greater efficacy.

### BISMUTH

In this country bismuth has practically replaced mercury as the drug to be alternated with courses of arsenic, or to be given with arsenic as the case may be. Furthermore, it is used almost exclusively in those syphilitic manifestations for which arsenic may be contraindicated. In its effect upon the *T. pallidum*, bismuth stands between arsenic and mercury in efficiency.

**Therapeutic Action of Bismuth.** It is known that the use of bismuth alone in the treatment of syphilis will result in a gradual disappearance of treponemata from the lesions and in their healing. However, this occurs much more slowly than under arsenic therapy. With the latter, infectious lesions heal in a time interval measured in days, with bismuth the healing period is numbered in weeks. Furthermore, in acute syphilis reversal of the blood tests takes place much more slowly with bismuth therapy alone than with arsenic. Another point worthy of note is that relapse occasionally occurs during the first course of bismuth which follows upon the introductory course of arsenic therapy in acute syphilis.

The mechanism of therapeutic action is not understood at the present time. Experimental studies are contradictory. It has been felt by some students that the action of bismuth is treponemistatic as shown by the classic experiment of Kolle: if a store of insoluble bismuth is deposited in

a rabbit's ear, inoculation of *T. pallidum* into the animal's testicle will not result in a chancre. However, if the ear with its store of bismuth is amputated later, a chancre subsequently develops indicating that bismuth holds the infection in abeyance but does not eradicate it. A similar situation has been reported in a study in which prostitutes in some districts in France were given bismuth regularly as prophylactic treatment. It was found that when this was stopped, some of the women developed the manifestations of secondary syphilis. Other investigators, not being able to demonstrate a treponemicidal effect of bismuth salts *in vivo* or *in vitro*, feel that these compounds unite in some way with certain tissue or humoral substances in the body to form effective therapeutic agents. It has been postulated by some that heavy metal may stimulate "tissue resistance". Recently Eagle reported that he found bismuth to be treponemicidal *in vitro* in dilutions comparable to those found in the blood stream of treated human beings. He found water soluble bismuth preparations treponemicidal in 1:50,000-1:225,000 dilutions.

**Bismuth Preparations and Their Use** From a pharmacologic standpoint several facts relative to bismuth are of importance. Bismuth preparations may be divided into those which may be dissolved in water and are thus administered in aqueous solutions, and those insoluble in water and therefore injected in an oily preparation. Some of the latter are soluble in oil, and others are merely suspensions of salts of bismuth in oil. Water soluble bismuth is rapidly absorbed, reaches a high peak of concentration in the blood, and is rapidly excreted. The bismuth of the oily preparations is slowly absorbed, does not reach so high a concentration in the blood, and is slowly excreted. Two thirds or more of injected bismuth is excreted in the urine, the remainder in the feces. After an intramuscular injection of bismuth in oil, excretion begins in twenty four hours, and continues for a month or more. In the body, bismuth is stored in most of the tissues. The prolonged depot of bismuth in oil in the gluteal muscles may be demonstrated by roentgenologic examination. Sometimes, however, such areas are walled off by a foreign body reaction and therefore may not constitute an active deposit from which bismuth may be absorbed. In general the form in which bismuth is used (aqueous or oily preparation) is rather immaterial provided injections are frequent enough and proper dosage is used. Bismuth should be given in such amount and often enough to maintain the urinary excretion of metallic bismuth at about 2-4 mg. daily.

Since water-soluble bismuth is more rapidly absorbed from the muscle it reaches a peak level in the blood within twenty four to thirty-six hours and then drops off as rapidly. Thus, under circumstances in which high levels are desired such a preparation may be used, but in order to maintain

a proper therapeutic level injections must be given about every third day. Water-soluble bismuth may be indicated at times in acute syphilis, especially if arsenic cannot be used. In pregnancy, for the same reason, aqueous bismuth may be used if only a short time is available for treatment before delivery. It may be used when rapid resolution of a tertiary process is desired, but fear of a Herxheimer reaction militates against the immediate use of arsenic. In general, the only preparations are the more practical for a number of reasons. Since bismuth in oil necessitates fewer injections for the maintenance of a proper bismuth level in the blood, its use is indicated in the average venereal-disease clinic where weekly attendance is all that can be asked of the patient. Also in cases where there is a probability that treatment will be irregular, bismuth in oil stands ahead of aqueous bismuth in offering greater protection against relapse to the patient because of its slow absorption and excretion.

The practitioner is offered such a variety of bismuth preparations with varying claims that he may have difficulty in making a choice. Each drug house offers and urges one or more bismuth preparations. Here, as is true with respect to all drugs, a safe rule to follow is to use only preparations which have been passed by the Council of Pharmacy and Chemistry of the American Medical Association. A question regarding this point should be asked of every drug "detail man" who urges the use of his bismuth preparation.

**WATER-SOLUBLE SALTS** If there is reason to use a water-soluble salt, tartrate, thioglycollate, or iodobismuthite may be used, with the realization that injections must be given every other day or every third day.

**BISMUTH IN OIL** is the preparation to be recommended most strongly for reasons noted above. It is recommended by the United States Public Health Service. Since most syphilitics in this country are treated in public clinics, the bismuth preparations to be used will be those furnished by the respective state health departments. Bismuth in oil is the choice of the state health departments.

**BISMUTH SALICYLATE IN OIL**, 0.13-0.2 Gm per dose (gr. 11 or 0.13 Gm U.S.P.) given intramuscularly (into the gluteal muscles) at five- to seven-day intervals is the preparation of choice\*. Courses of bismuth should consist of from six to fifteen weekly injections depending upon the stage of the disease.

In recent years a bismuth preparation which has been shown to have some effect by mouth has been placed on the market. Its use in adequate dosage may be attended by some gastro intestinal symptoms. We do not

\* The content of metallic bismuth varies somewhat in the various products on the market. Unquestionably the rate of absorption varies as between the various products as well as in patients.



feel that, as a general rule, it has any place in the treatment of syphilis. The physician must know whether the patient is receiving his treatment, and can be certain of this only if the bismuth has been placed in the muscle. Such knowledge would not be available in the case of oral administration without studies of urinary bismuth excretion.

**Technic of Bismuth Administration.** The oily suspension of bismuth must be well shaken before its aspiration into a syringe. If shaking is not thorough, much of the bismuth will remain in the bottom of the bottle. The preparation is drawn into a 2-cc syringe in such quantity that the adult obtains the dosage as indicated above. The needle used for injection should be of 18-20 gauge, and from 2 to 2.5 inches in length. In very obese persons even longer needles may be necessary.

The best position for the patient receiving the intramuscular injection of bismuth is prone on the examining table, with feet hanging over the end, and the toes turned in. In this position the gluteal muscles are relaxed and the pain of injection will be less. (In clinics where many patients are treated it is not customary to use this position because of the need to conserve time as well as linen. Under such circumstances, although muscular relaxation is not attained so well, intramuscular injections are given in the upright position.) The injection should be made in the upper outer quadrant of the buttock close to the point where the four quadrants meet. Injection at this site avoids an infiltration about the sciatic nerve, and discomfort upon sitting. The oily solution or suspension must be injected deeply into the muscle. Superficial injections within the fat may lead to painful nodules, and at times to sterile abscesses. The syringe may conveniently be held in the manner of a dart about to be thrown. The site for injection is cleansed with alcohol, the left hand draws the buttock downward, and the needle is quickly plunged through the skin and deep into the muscle. Traction is made upon the plunger for several seconds to be certain that a blood vessel has not been entered. (If blood is obtained another site must be selected.) The injection is made slowly and should require little pressure upon the plunger. After rapid removal of the needle, the attendant or patient massages the area for several minutes with an alcohol sponge. Some therapists recommend the injection of about 1 cc of air to empty the needle of the oily mixture before its withdrawal through the superficial tissues. This is not essential. The injection should be given into the same buttock on alternate weeks.

**Indications for Bismuth.** These are the indications for a heavy metal, and will be explained in the treatment plans offered in the subsequent chapters. Bismuth is recommended almost universally in preference to mercury, for it has fewer drawbacks than the latter.

**Untoward Effects.** UNTOWARD LOCAL EFFECTS usually can be avoided

by proper injection technic. These effects are sciatica, painful nodules, and sterile abscesses due to tissue necrosis. Injection of an oily mixture into a vein may produce oil embolism with death. If the suspension is injected into an artery there is severe pain. Mottling of the skin supplied by the artery, with subsequent necrosis and sloughing, is the usual accompaniment.

**BISMUTH DEPOSITS** Since bismuth is excreted so slowly there is naturally a cumulative effect of the metal, and constitutional reactions may occur some time after the institution of treatment. The most common result of this cumulative effect is a deposit of the metal in the mucous membranes of the mouth. This is seen most frequently at the gum margins, as a black stippled line similar to that seen in lead poisoning. Such a deposit is aggravated in patients who have poor dental hygiene and gingivitis. With prolonged administration, as with fifteen to thirty injections in a series, bluish-black deposits may be seen in the mucosa of the tongue, lips, gums, palate, and mouth. These may persist for months after treatment is stopped, or may even be permanent to some degree. In the presence of poor dental hygiene, an actual gingivitis with ulceration may occur at times. This could probably be avoided with proper dental care, but in the economic stratum in which syphilis claims its greatest toll, such ideal conditions are not to be found. In any event, the gingivitis and stomatitis encountered with bismuth are not so severe nor so frequent as those in the days when mercury with its similar reactions was commonly employed.

**SKIN ERUPTIONS** are rare with the use of therapeutic dosages of bismuth. These have been described as erythema, urticaria, and papular eruptions simulating pityriasis rosea. We have seen an occasional instance of the latter. We also have seen mild exfoliative dermatitis follow the use of bismuth too soon after the patient's recovery from a severe exfoliative dermatitis due to an arsenamine. The subsequent use of bismuth is unattended by dermatitis.

**GASTRO-INTESTINAL REACTIONS**, such as nausea, vomiting, and diarrhea, have been reported. It has been said that hepatitis may occur following the use of bismuth, and that this heavy metal might be implicated in the production of portal cirrhosis. However, it may safely be said that untoward reactions in the gastro-intestinal tract must be excessively rare. We give thousands of injections of bismuth in our clinic annually without seeing these manifestations.

**OTHER EFFECTS** Although it might be expected that this heavy metal would cause nephrosis, albumin and casts in the urine are rare. Occasionally patients receiving bismuth complain of weight loss, low-grade fever, and aching in muscles and joints. The explanation of these by-effects is

not clear Cessation of treatment may be necessary at times because of these symptoms

**Contraindications to Bismuth Therapy.** Under few circumstances is bismuth contraindicated In the rare case of cutaneous reaction its further use may seem unwise Possibly in portal cirrhosis one might hesitate to use it Renal disease may be a contraindication, especially acute nephritis or nephrosis

### MERCURY

Historically, this metal is of interest since for centuries it was the only effective agent available for use in the treatment of syphilis Following the introduction of arsphenamine by Ehrlich, mercury was still important for use in some of the manifestations of late syphilis, and for use in courses alternating with those of arsenic In the past two decades, it has been almost universally replaced by bismuth However, the metal still has a place, as will appear later

**Therapeutic Action of Mercury** As in the case of bismuth, the way in which this metal acts is not known It is well known, of course, that mercury salts are highly toxic to protozoa as well as bacteria, but only in concentrations toxic to the host also Healing of acute lesions of syphilis occurs under mercury therapy, but the lesions are reported to remain darkfield positive for a long time, and thus it may merely hasten the healing which would occur spontaneously Stokes feels that mercury is a "builder of tissue resistance" Moore believes that since there is little evidence to substantiate this, mercury probably acts by some degree of treponemistatic effect—a reduction in multiplication of organisms so that host immunity may be built up and have an opportunity to be effective

**Mercury Preparations and Their Use** Mercury has been used by mouth for centuries It is rapidly absorbed from the gastro intestinal tract Another old method of administration is by inunction That this method is effective is proved by the toxic effects which can be produced by absorption of the metal through the sweat glands and hair follicles These older methods of administration are still used under circumstances to be indicated below

Modern treatment with mercury has consisted of the use of aqueous solutions or oily suspensions given by injection Mercury is rapidly absorbed and soon appears in the urine, which is the main route of excretion, although some leaves in the feces To be therapeutically effective the frequency of administration and size of the dose must be such as to give a daily urinary excretion of about 1 mg Thus, incidentally, is a sufficiently toxic dose to produce a mild stomatitis

*Mercury by mouth in the treatment of syphilis is inexcusable except in the*

*child and in the aged under particular circumstances* Mercury and chalk is commonly used by mouth in the treatment of syphilis in infants. In the aged, for symptomatic relief of tertiary lesions, especially the benign ones, the old "mixed treatment" may be used in a preparation as follows

Mercury bichloride	gr ii	13
Potassium iodide	oz ii 60	
Syrup of sarsaparilla	oz iv 120	

Sig One teaspoonful three times daily

Protiodide of mercury pills, gr  $\frac{1}{6}$ - $\frac{1}{2}$  (0.01-0.03 Gm) three times a day may be used under the same circumstances

*Inunctions of mercury have no place in the treatment of early syphilis* At times the administration of mercury via the skin is permissible. As in the case of mercury by mouth, it has a place in the symptomatic relief of the aged patient who is suffering from late benign lesions of syphilis. In the aged (because of malnutrition, tissue atrophy, and debility) intramuscular injections of bismuth may be contraindicated. Mercurial inunctions fill the need for mild antisyphilitic treatment. In rural regions of the South, transportation of patients for antisyphilitic treatment is at times almost impossible. We feel that in late syphilis we are justified in making a compromise as follows—if the patient will arrange to visit our clinic weekly during the courses for the injections of arsenicals, he may take the heavy-metal course at home by the inunction method. *This plan is not to be countenanced in early syphilis*. In late cases of syphilis where only heavy-metal therapy is to be used, mercury inunctions may be used to alternate with courses of bismuth.

**Administration INUNCTION** Instruction for mercurial inunctions is somewhat as follows. A "rub" must be taken nightly for six days. None is taken on the seventh, but a bath is ordered for that day. The ointment used is *unguentum hydrargyri fortius* (blue ointment) U S P which contains 50 per cent by weight of metallic mercury. An amount of slightly less than a level teaspoonful is used for the inunction each day. The ointment is rubbed into the selected area of skin with the palm of the hand, for *twenty minutes by the clock*. The rubbing should not be done with too much pressure and the area selected should be relatively hairless to minimize the danger of dermatitis and folliculitis. The area of skin into which this amount of mercury ointment is rubbed should be as large as the flat of the hand and should be used no more often than at weekly intervals. Therefore the patient is usually advised to use skin areas as follows: first night, left upper arm, second night, right upper arm, third night, left axilla, fourth night, right axilla, fifth night, inner aspect left thigh, sixth night, right thigh. For the seventh night, a hot bath with soap and water is advised. The next week this regime is repeated.

In using the axillae the ointment should not be rubbed into the axillary fossa because of the hair, but below this on the lateral wall of the chest at the level of the fourth to sixth ribs. If the thighs are too hairy, the skin of the abdomen may be used. It is advisable that the patient wear the same underwear all the week because a certain amount of mercury will thus be rubbed in, especially in the winter-time, if woollen underwear is worn. Either printed instructions should be given the patient, or he should repeat back the instructions in detail to the advising physician. The main objection to the use of mercurialunctions is that it is dirty, and permits the patient's associates to guess the presence of his disease.

**FOR INJECTION** there are several aqueous solutions of mercury salts, which may be given intravenously and intramuscularly. These have no place in the treatment of syphilis under ordinary circumstances. Such preparations must be given daily or every other day. Intravenously they lead to thrombosis and may be dangerous to life, intramuscularly they are very painful and patients usually will not tolerate them. Oily suspensions of insoluble mercury salts should not be used because of a possible cumulative toxic effect due to their slow absorption. Their use also may lead to fibrosis of the muscles of the buttock.

**Indications for Mercury.** The indications are those for heavy metal in general except that mercury should be substituted for bismuth but rarely. Because of its effectiveness by mouth, it has its specific indications in the infant and in the aged, in the latter for symptomatic relief and because of the impracticability of giving bismuth intramuscularly. Mercury is indicated for alternation with courses of bismuth in conditions where arsenic therapy is contraindicated. These indications will be pointed out in subsequent treatment outlines.

**Untoward Effects.** Mercury, a cumulative poison, has more serious untoward effects than does bismuth. Stomatitis, with ulceration, sore and tender gums, and loosening of the teeth, is not infrequent. Abdominal pain and diarrhoea may occur. A tubular nephrosis with albuminuria and casts may occur. The appearance of any of these by-effects demands the immediate cessation of the use of mercury. (In contrast to bismuth, mercury may lead to permanent changes in the gluteal muscles due to fibrosis.)

**Contraindications to Mercury.** Renal disease contraindicates the use of this therapeutic agent.

## IODIDES

The salts of iodine have been used in the treatment of syphilis for about one hundred years.

## THERAPEUTIC ACTION

Iodides are used empirically. Certainly they have no treponemicidal effect, and are of value merely in their resorptive action. This action occurs in any granulomatous process, such as tuberculosis, fungus granulomas, and the like. The syphilitic gumma may resorb under iodide therapy alone. In addition, better penetration by the antisyphilitic drugs occurs so that they may be more effective against the treponemata in the lesion.

**Preparations and Use** There are many salts of iodine but there is no reason to believe that one is more effective than another. Absorption from the gastro-intestinal tract is rapid, almost complete, and excretion is complete in three to four days. The potassium or sodium salts of iodine are the cheapest, and most readily available. The former is in common use, and is given in from 10 to 25 gr (0.65 to 1.6 Gm) doses three times a day. It may be prescribed in an aqueous vehicle. In common use is the saturated solution, containing approximately 1 gr per drop, taken in water. Sodium iodide has been used intravenously in neurosyphilis by some physicians.

**Indications for Iodides** Since iodides are of value in the resorption of granulomatous processes, they have little place in the treatment of acute syphilis. Exceptions will be found in treatment resistant cases, and in precocious tertiaryism due to inadequate therapy. Iodides do have a place in the treatment of all late manifestations of syphilis, and especially in the first few weeks of the treatment of such conditions. A resolution of late syphilitic inflammations will possibly diminish the possibility of a Herxheimer reaction when arsenic is employed later. Furthermore, resolution of gummatous reactions will permit penetration of the antisyphilitic drugs into these areas. Especially is this true in visceral and central nervous system syphilis.

**Untoward Effects** Iodides often cause patients to complain of a burning sensation in the epigastrium, and acid eructations. These can be avoided to some extent by giving the drug after meals, and by reducing the dose. Of more serious nature are coryza, edema of the tongue, larynx, nasal mucosa, eyelids, and at times generalized edema, which necessitate stopping the drug. Fever may be caused by iodides. Salvation, and swelling and pain of the salivary glands may occur. Not infrequently an acne form eruption appears, at times chronic hypertrophic or verrucose skin lesions may occur.

**Contraindications to Iodides** Iodides should not be used in the syphilitic patient in the presence of thyrotoxicosis or active pulmonary tuberculosis.

## FEVER THERAPY

Fever therapy is limited, in actual practice, to the management of neurosyphilis and syphilis of the eye. Since it requires hospitalization of the patient and observation by trained personnel, a detailed discussion of this type of treatment can serve no good purpose here. Only such points will be discussed as may serve to answer general questions, together with something of indications and contraindications.

It has long been known that febrile diseases have a beneficial effect on general paresis, and it is of interest that steam baths were used several hundreds of years ago in conjunction with mercury inunctions. Wagner von Jauregg, who had been experimenting with various methods of producing fever, in 1917 inoculated tertian malaria in a group of patients having general paresis. In the next decade several authors reported that fever had a beneficial effect in neurosyphilis. Subsequent to these reports methods of producing hyperpyrexia by artificial means were developed.

## THERAPEUTIC ACTION OF FEVER

The therapeutic effect of fever upon syphilitic processes is not clearly understood. Several explanations have been offered by various workers in the field.

One theory is that the fever is directly treponemocidal. Warren and his collaborators found that treponemata die if kept at 107.6° F. for one to six hours, *in vitro* or *in vivo*. Whether such apparent facts can be transferred directly to the disease in the human subject is not certain. In a study carried out in collaboration with Warren and his group we used hyperpyrexia, produced by radiant heat, in acute syphilis. Although we could demonstrate the disappearance of the treponemata from superficial lesions after six to eight hours in the cabinet, and though the lesions healed as rapidly as after arsenic therapy, subsequent relapse occurred in 75 per cent of the cases. In our studies, a temperature of 106.8° F. was maintained for from fourteen to sixteen hours. Obviously, such prolonged temperatures do not kill all the organisms in the body. Other theories, some with experimental evidence in their favour, are numerous. Hyperpyrexia produces profound changes in tissue metabolism which may play a part in the host's reaction to infection. The changes in vascular permeability and reactions about areas of inflammation may be factors in the good effects of hyperpyrexia. Some investigators believe that fever has an important effect on immune reactions, as it shown by the increased production of antibodies, changes in the reticulo-endothelial system, and an increase in proteolytic and lipolytic enzymes.

**Methods.** Several methods have been introduced to produce fever

Opinions regarding the type of fever therapy to be employed have varied greatly. Malaria was the method of choice originally, and it is still considered to be the best by some syphilologists. Tertian malaria is most commonly used. In recent years quartan malaria has been used more commonly in the Negro, because of some degree of natural immunity to tertian malaria.

Artificial methods of producing hyperpyrexia include the Kettering hypertherm, radiant heat, diathermy, and short-wave induction. Hot baths and typhoid vaccine have been used.

As was indicated above, the details of the inoculation of malaria or the production of artificial fever will not be discussed here.

The Co-operative Clinical Group studies of the use of fever therapy in neurosyphilis are worthy of brief summary. Clinical results in general paresis were similar with both the natural- and artificial-fever methods. The incidence of treatment deaths in malaria was 13 per cent, with artificial hyperpyrexia 8 per cent. After remission following fever therapy, relapse was no greater with one method than another. Artificial-fever therapy was used for periods of several hours at about 105° F. In this study, "the highest percentage of clinical remissions was obtained in patients treated with an average of sixty-nine hours of fever above 101° F, of which total fever time 70 per cent was at a level of about 105° F with a maximum temperature of 106.9° F. Equally good results were obtained in patients treated with an average of forty-four hours of fever above 101° F, of which total time 57 per cent was above 106° F with a maximum temperature of 107° F."

**Indications for Fever Therapy.** Neurosyphilis is practically the only condition for which fever therapy is indicated. The several types of central-nervous system syphilis for which fever therapy should be used will be indicated in the chapter dealing with these manifestations of syphilis.

**Untoward Effects.** Fever therapy is attended by certain dangers. It may be used only after a careful evaluation of the physical status of the patient. In addition to a routine physical examination, this should include roentgenologic study of the heart, an electrocardiogram, blood counts, renal-function tests, blood nonprotein-nitrogen and liver-function tests.

One result of twelve to sixteen paroxysms of malaria may be a rather marked anaemia. Cachexia and debility may occur. Cardiac failure is seen occasionally. Rupture of the spleen has been reported several times. (Recently it has been shown that the severity of the course of malaria can be regulated to some extent by the use of intramuscular injections of water-soluble bismuth which controls the number of paroxysms.)



Apparently gummatous lesions, especially of the skin, may appear after fever therapy, as an unexpected complication

With artificial fever therapy the degree of fever can be regulated at will, and can be terminated at any time. A temperature of over 106.5° F. is associated with definite hazards and possible permanent cerebral damage. Without careful control of fluid balance, renal 'shut-down' may occur. We have seen cerebral thrombosis, also sudden death.

**Contraindications to Fever Therapy** The presence of one of a number of the degenerative diseases contraindicates the use of fever therapy. The more common ones are chronic nephritis, hepatic disease, diabetes mellitus, and generalized arteriosclerosis. Hypertension, pulmonary tuberculosis, bronchiectasis, malnutrition, and general debility also rule out this method of treatment. Though physiologic age is of greater importance than chronologic age, it may be said that, in general, patients over fifty years of age are not good risks for fever therapy. However, the individual patient must be evaluated. We have successfully treated patients more than fifty five years old.

### JARISCH HERXHEIMER REACTION

In the preceding sections of this chapter the untoward effects of the various drugs have been indicated. Such reactions are due to the drugs *per se*, and will be just as likely to occur in nonsyphilitic as in syphilitic patients.

The Jarisch Herxheimer reaction is a treatment reaction related to the disease and not the drug. It is believed that the tissues of the host are sensitized to the *T. pallidum* or its products, when these are destroyed. As the result of the use of antisyphilitic drugs, accentuation or aggravation of the inflammatory reaction occurs at the syphilitic focus. Moore compares this in a way with the focal, local, and systemic reactions which occur upon the intracutaneous injections of tuberculin in a tuberculous individual.

Many physicians are dubious about the occurrence of such a reaction since it has never fallen within their experience. The most frequent demonstrable Herxheimer reaction occurs in acute syphilis. In the presence of a chancre of some weeks' duration, an injection of arsenic may be followed in some hours by the appearance of the macular rash of secondary syphilis. In established secondary syphilis, an injection of arsenic may be followed by intensification of the rash, elevation in temperature, malaise, aching of joints and muscles, and even swelling of joints. One may see cases in which, within twenty four hours after the injection of an arsphenamine, a papular rash becomes pustular, with small centres of necrosis which are sterile. These may well represent an intense reaction in the

papule resulting in necrosis due to vascular occlusion and infiltration by inflammatory cells

Since tissue involvement in acute syphilis is diffuse and not dangerously infiltrative, the Jarisch-Herxheimer effect is of no practical significance in early syphilis. If one visualizes extensive localized syphilitic inflammatory foci, strategically placed with reference to vital organs, such reactions may be dangerous or even fatal. These will be encountered especially in late syphilis. Others may be of little significance, as the increased pain and swelling in tertiary syphilis of the bone.

Arsenic being more treponemicidal than bismuth, it is more likely to be followed by a Herxheimer reaction than is bismuth. Thus after an injection of an arsphenamine we have seen such a reaction in an unsuspected tertiary process in the larynx require tracheotomy in order to prevent death from asphyxia. We have encountered hemiplegia due to an intensified reaction in syphilitic endarteritis of the brain after treatment. Rupture of the aorta in aortitis or aneurysm has been reported following the injection of arsenic. In our experience anginal pain has developed upon treatment, which can be interpreted as probably due to a reaction in a syphilitic plaque about the orifice of a coronary artery. Sudden death has been reported with this as a possible basis.

Though a Jarisch-Herxheimer reaction from bismuth therapy is rarely of such severity as to attract attention, an exceptional instance may be encountered as in Case 8. Had arsenic been given in this case, asphyxia would have undoubtedly occurred.

**Case 8** A thirty-five year-old married Negress was first seen in the Syphilis Clinic because of a doubtful Kahn test. The Wassermann test was negative. Shortly after her first marriage, her husband developed a genital lesion. Some months later she suffered from "rheumatism" which involved all her joints. Her blood was found to be positive, and a physician gave her eight intramuscular injections. All blood tests subsequently were said to be negative. On the basis of this history the patient was placed on antisyphilitic treatment, but lapsed after four injections of bismuth.

Two years later she was referred to the Syphilis Clinic because of *iritis* of the right eye. Other than for the mild *iritis*, the physical examination was negative. The blood Wassermann test was repeatedly negative, but the Kahn test consistently positive. The spinal fluid was negative.

The *iritis* subsided before antisyphilitic treatment was begun. Two days after her first injection of bismuth in oil she developed hoarseness. Ten days after the injection, examination by the otolaryngologist revealed "Marked bilateral supraglottic infiltration obscuring the vocal cords. The masses are pale, with superficial ulceration. The epiglottis is thickened, and there is interarytenoid infiltration and edema." This examiner noted the absence of active inflammation of acute infection, and felt that the appearance of the lesion suggested syphilis.

He thought this represented a Herxheimer reaction (The patient had not had any iodide) The stridulous breathing was audible throughout the clinic waiting-room Examination of the larynx was repeated every few days Little improvement occurred for ten days, then treatment with bismuth was resumed Gradual improvement took place, though much infiltration of the laryngeal structures still was present four weeks after the appearance of symptoms

The patient was then not seen for three months, at which time there was some moderate interarytenoid thickening Treatment was resumed and continued for some months before it was lapsed again

**Comment.** The iritis was probably not of syphilitic origin, for it cleared too promptly without treatment The laryngeal reaction in an apparent latent syphilitic state represented a Herxheimer reaction due to bismuth therapy Definite laryngeal obstruction was thereby produced

Since the Herxheimer reaction is so much more likely to occur with the use of arsenic, the treatment of syphilis, if the disease is of more than a couple of years' duration, always should begin with an introductory course of bismuth and iodides Several weeks of bismuth and iodides permit at least some resolution and absorption of tertiary syphilitic inflammations Not only is such treatment indicated in the presence of known late syphilis, but also in late latency because of the possible presence of unsuspected tertiary lesions

### THERAPEUTIC PARADOX

This term has been applied to the fibrosis and scarring that result from the resolution of a late syphilitic inflammatory focus Tertiary lesions are associated with tissue destruction and heal with a deforming scar

Since a Herxheimer reaction may occur at a syphilitic focus, it is obvious that it may lead to more intensified tissue destruction, and thus to a greater scar (This may be compared to the tissue necrosis occurring at times at the site of a tuberculin test in a very tuberculin-sensitive patient) Therefore, the objective of treatment should be to obtain resolution and absorption of the syphilitic focus with a minimum of reaction Thus, to reduce the "therapeutic paradox" to a minimum in tertiary syphilis, it is advisable to give a preparatory course of iodides and bismuth before arsenical compounds are used in treatment Case 84 probably represents a therapeutic paradox (The resolution of a syphilitic plaque at a valve commissure with resultant distortion led to aortic insufficiency)

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## VI

### PRIMARY SYPHILIS

#### HISTORICAL NOTE

ACCORDING to Pusey, the chancre was established as the primary lesion of syphilis by Fernel in the sixteenth century. Others emphasized the firmness of the chancre and the indolence of the bubo a century and more before Hunter, thus differentiating syphilis from other genital diseases. By the famous experiment on himself in 1767, John Hunter beclouded the whole issue. He believed the etiology of gonorrhea and syphilis to be the same, the former representing involvement of a mucous membrane—a "secreting surface," and the latter of the skin—a "nonsecreting surface." In an attempt to prove this, Hunter inoculated his skin with gonorrheal pus, and apparently with syphilis as well since he developed this disease, thus apparently proving his point. It was well into the nineteenth century before gonorrhea, syphilis, and chancroid were established as disease entities. Ricord was instrumental in breaking down the misconception dating from Hunter's misinterpretations.

If the *T. pallidum* gains entrance to the tissues of the host, a lesion appears in most instances at the site of inoculation after a variable period of incubation. This first recognizable evidence of syphilis in the patient constitutes the chancre—the initial or primary sore.

#### INCUBATION PERIOD

The incubation period of the chancre is variable. It may be as short as eight to ten days, or as long as sixty days, and, rarely, longer—as much as ninety days. The majority of chancres will appear within ten to twenty days following exposure. Case 9 illustrates a long incubation period.

**Case 9** A thirty-seven-year-old, white, married carpenter entered the Syphilis Clinic because of a penile lesion. Exactly two months previously he had had one extramarital exposure. A small lesion was noted on his penis twelve hours before visiting the clinic.

Examination revealed two small moist papules 3 mm. in diameter, one at the corona on the dorsum, and one at the frenum of the glans. There was no induration and no lymphadenopathy. *T. pallida* were found by darkfield examination. The blood was seronegative on two occasions.

The date of the darkfield examination was February 6th. From then until May 7th the patient received arsphenamine 0.3 Gm.  $\times$  5, neoarsphenamine 0.6 Gm.  $\times$  3, mapharsen 0.06 Gm.  $\times$  1, and bismuth  $\times$  7. Treatment was taken regularly. All blood tests were negative. The lesions were healed after two injections.

Because the patient's wife was ill in the hospital, sexual intercourse took place only once between the extramarital exposure and the appearance of the lesions. This was on February 3rd. The wife's blood was still negative on March 18th and 25th. She failed to return for further check up until May 6th, at which time she was found to be seropositive. Furthermore, she presented a maculopapular rash of two weeks' duration. Moist papules on the vulva contained *T pallida*.

**Comment.** If the history can be accepted as accurate, this case demonstrates that the incubation period of syphilis may be as long as two months. The penile lesions no doubt were so early that neither induration nor lymphadenopathy had developed. Serologic tests were done on two samples of blood. These lesions represented very early seronegative primary syphilis. Of further interest is the fact that the wife had developed neither a recognizable primary lesion nor a positive blood at the end of a seven week period after one exposure to the infectious lesion. About six weeks after this, she was seen in the secondary stage of syphilis. There is no reason to believe that the husband was again infectious, as he was under regular treatment and was always seronegative.

## PATHOLOGY

In its earliest form the primary lesion appears as a papule which represents a fluid and cellular exudate. Endarteritis is present in the smaller blood vessels, this is proliferative and goes on to obliteration of the lumina of the vessels. A perivascular infiltration of round cells (plasma cells and lymphocytes) occurs. Fibroblastic proliferation is prominent and accounts for the hardness of the fully developed chancre. The treponemata multiply and lie in the perivascular lymph spaces. Healing takes place by fibrous-tissue replacement, with or without scarring of the skin.

## SITE

Primary lesions of syphilis in most instances occur on or about the genitals. Some authors estimate that about 95 per cent of chancres are found about the genitalia. Among the more than six thousand cases on record at the Vanderbilt University Hospital Syphilis Clinic, there were four hundred and sixty-three patients with chancre. Of these primary lesions, including those already accompanied by secondary lesions, twenty-five appeared at sites other than the genitalia. Thus in our cases the incidence of extragenital chancres was 5.5 per cent. The distribution of extragenital lesions is shown in Table VII.

TABLE VII

DISTRIBUTION OF EXTRAGENITAL CHANCRES BY SITE, RACE, AND SEX

Site	Males		Females	
	White	Negro	White	Negro
Lip	5	3	3	2
Tonsil	-	-	1	1
Tongue	1	-	-	-
Mouth	-	-	1	-
Nose	-	-	1	-
Breast	-	-	1	-
Wrist	-	-	1	-
Finger	-	1	1	-
Abdomen	2	-	-	-
Groin	-	1	-	-
Totals	8	5	9	3

## THE CHANCER

## CLINICAL CHARACTERISTICS OF THE CHANCER

Several authors estimate that about 90 per cent of initial lesions are "typical," and that the remainder do not show the usual characteristics. The site of the lesion to some extent determines its characteristics.

The *typical* or so-called Hunterian chancre appears first as a red papule with relatively little induration. The surface of the papule becomes eroded rather than ulcerated, and increases to the size of the primary lesion (In our weekly observation of the contacts of acute cases of syphilis we have been able to follow this earliest phase of the chancre.) As a rule, the lesion is more advanced, of five or more days' duration, before it is seen by the attending physician, unless he is engaged in the active tracing of contacts. By this time it may have reached a diameter of from 3 or 5 mm. to 2 cm., or even larger.

As the chancre reaches its full development it presents the following characteristics. It is almost always a solitary lesion. The ulcer, or less commonly the erosion, has a clean appearance, without a purulent exudate. Often it is covered with a thin crust from the drying of the serous exudate, upon the removal of the crust the lesion may be found to be quite dry. Bleeding, upon removal of the crust or following irritation, such as scraping or rubbing to obtain material for darkfield examination, is relatively slight. The borders of the chancre are even and rolled. Upon palpation with the gloved fingers the base of the lesion is found to be hard, frequently of a

cartilaginous consistency. It is often described as giving the sensation of a button in the skin. The firmness of the lesion can often be well demonstrated in chancres involving the prepuce, since upon retraction the lesion may be seen suddenly to evert *en masse*, much like that of eversion of the upper eyelid. The initial sore is generally but slightly tender or painful. In contrast to certain lesions from which it must be differentiated, com-

FIG 6

FIG 7



FIG 6 Primary syphilis (Case 10)

FIG 7 Primary syphilis and chancroid (Case 11)

paratively little pain is experienced upon scraping the lesion for serum for darkfield examination. There is usually little edema about the sore, except when located on the foreskin and certain parts of the vulva. The uncomplicated chancre commonly heals spontaneously within ten to fourteen days, but may persist up to six weeks or more. Cases 10, 11, 12, and 13 represent 'typical' chancres.

**Case 10** A seventeen year-old white boy complained of a painless penile ulcer of three weeks' duration, which had appeared ten days after sexual exposure.

Examination showed a nontender, clean ulcer the size of a sixpence, the base was hard. Both groins contained enlarged nodes. Darkfield examination of material from the ulcer as well as from a lymph node, by puncture, demonstrated many *T pallida*. Blood Wassermann and Kahn tests were positive.

**Comment** The chancre in this case is an example of the typical lesion (Figure 6).

**Case 11** A twenty three-year-old white male had been exposed five weeks previously. About one week later he noted a 'pimple' on the glans, which ulcerated and was very painful. He treated the lesion with mercury bichloride.



A week or so after the appearance of this ulcer he developed a sore at the base of the penis. A week before admission to the clinic a bilateral lymphadenopathy appeared which became hot and painful.

Examination of the ulcer on the glans showed it to be 'punched-out,' tender, with a red border and purulent exudate on the base. The ulcer at the base of the penis presented an infiltrated base, had a crust, and was not tender.

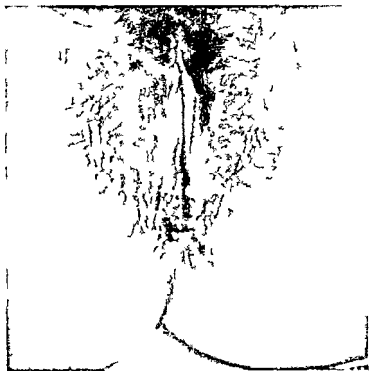


FIG. 8 Primary and secondary syphilis (Case 12)

Inguinal nodes were the size of walnuts. Upon darkfield examination, treponemata were found in the upper lesion, but none in the ulcer on the glans. Blood Wassermann and Kahn tests were negative.

**Comment.** This patient presented genital ulcers of more than one etiology, namely, a syphilitic chancre and a chancroidal ulcer (Figure 7).

**Case 12** A thirty year-old white married woman, separated from her husband, had her last sexual exposure eight weeks before admission to the Syphilis Clinic. Five weeks later she became aware of a genital sore which was somewhat painful to touch. However, she had noted inguinal adenopathy two weeks before the appearance of the sore. At about the time she first became conscious of the genital lesion, she developed headache and a rash.

Examination revealed a maculopapular rash involving the trunk, buttocks, arms, and palms. There was general glandular enlargement. A hard, tender

ulcer was found at the posterior fourchette, 1.5 cm in diameter. Serum from the lesion contained *T pallidum*. Blood Wassermann and Kahn tests were positive.

**Comment** Unquestionably the chancre was present before the patient was aware of it, for the patient's knowledge of it coincided with the development of the rash. The sentinel adenopathy had appeared two weeks earlier. Thus in-

FIG 9



FIG 10



FIGS 9, 10 Primary syphilis—multiple chancres (Case 13)

icates that primary lesions in women may be missed. A few of the secondary lesions on the buttocks may be seen faintly in the photograph (Figure 8).

**Case 13** A twenty nine year-old white man noted a small ulcer on the left side of the shaft of the penis 1.5 weeks previously. Two days after the appearance of the first ulcer, two more were found, one at the urinary meatus, and one on the right side. Enlarged inguinal nodes were apparent a few days after the penile lesions were seen. The first lesion was found two weeks after sex exposure.

On examination the adenopathy was evident. Each lesion presented a firm base, rolled indurated edges, and lack of tenderness. *T pallida* were found in each of the lesions. Blood Wassermann and Kahn tests were negative, and remained so under treatment.

**Comment** This case is an example of multiple chancres (Figures 9 and 10).

In the case of genital chancres variations from the usual may be encountered because of the site and complicating factors. Pain may be fairly prominent in chancres of the vulva, and edema may be greater than usual at this site. This is especially true in pregnant women in whom the labia are more turgid, probably accounting for the extensive edema seen at times. Chancre of the uterine cervix is probably more common than is

generally believed. Because of the firmness of this structure the hardness of the chancre may not be so obvious. Those who have studied the subject most say that chancre of the cervix may present itself as an erosion, ulceration, or induration of the cervix.

Secondary infection of pyogenic nature, simultaneous infection with the Ducrey bacillus of chancroid, and "chemical burns" from the application of iodine, phenol, mercury bichloride, etc., may alter the appearance of what might otherwise be a typical chancre. These bacterial or chemical factors may account for unusual edema, purulent exudate, bleeding, tenderness, pain, deep ulceration, extensive tissue destruction, and the absence of the characteristic hard base. In the male it is not unusual to see a balanitis if a chancre has developed on the glans or on the inner surface of the prepuce. Under such circumstances it may be impossible to retract the foreskin. Palpation of the glans and prepuce in such cases often reveals the characteristic induration of the chancre. Due to lack of cleanliness, accumulation of secretion, and often an attendant gonorrheal urethritis, marked edema and increasing phimosis may occur. Uncommonly a chancre may run its course without a break in the skin, thus without ulceration as in Case 14. In this patient all characteristics of the typical chancre were present except that the skin was intact over it, and only by scraping deeply through it could serum be obtained for darkfield examination. Atypical chancres are illustrated by Cases 15 and 16.

**Case 14** A thirty-year-old Negro developed a "bump" on the penis about two months before admission to the Syphilis Clinic. This gradually enlarged and flattened out to reach the size of a threepenny bit. The skin was never broken, but was scaly. Nodes became enlarged in both groins a week before admission. At this time two blood tests were negative.

Examination showed bilateral inguinal adenopathy, each the size of a lime. The penile lesion was the size of a threepenny bit, hard, non tender, moved with the skin, and not ulcerated. It was necessary to break the skin to get serum for demonstration of *T pallidum* by darkfield examination. Blood Wassermann was doubtful, Kahn test positive.

**Comment.** This chancre had been present for a time without ulceration, and probably would have remained so. If the history were acceptable, this case might be an example of delay in the development of a positive blood test. Complete healing occurred within ten days after two injections of an arsenical (Figure 11).

**Case 15** A twenty-six-year-old white man had had one extramarital contact six weeks before. Four weeks later he noted a painless "pimple" which he squeezed. An ulcer appeared which increased in size and drained profusely.

Examination revealed a superficial ulcer the size of a half-crown on the shaft of the penis. It was moist, had a clean margin, was not tender, and presented no induration. Bilateral inguinal adenitis was present. Many *T pallida* were

found upon darkfield examination. Blood Wassermann and Kahn tests were positive.

**Comment.** This is an example of an atypical chancre. Healing was prompt under treatment (Figure 12).

**Case 16.** A twenty-five-year-old widow was seen in the Gynecology Clinic on January 10th because of trichomonas vaginitis, and at this time had negative

FIG. 11



FIG. 12



FIG. 11 Primary syphilis (Case 14)

FIG. 12 Primary syphilis (Case 15)

blood tests. She re-visited the clinic on January 31st because of a genital lesion. Shortly after the first visit she noted the gradual development of an enlarged inguinal node.

Examination showed a soft, red, moist, granulomatous lesion on the right labium. It was 2 by 4 cm. in size. A smaller "kissing" lesion was opposite it on the left. The right inguinal node was enlarged. Darkfield examination of material from the tumour showed many *T. pallida*. Blood Wassermann and Kahn tests were positive.

**Comment.** The appearance of the lesion not only misled the gynecologists, but also a dermatologist, who suggested a biopsy. The patient was persistent in denial of sexual exposure, but under direct questioning admitted she "almost did," expressing surprise that infection was possible without the sexual act. Thus the need for careful history-taking so that contacts may be traced is shown (Figure 13).

Occasionally multiple chancres appear as the result of the contact of the chancre with adjacent skin areas. Thus a second, "kissing" chancre may appear on the labium minor or majus opposite the initial lesion (Case 16).

Likewise a second chancre may appear on the scrotum in apposition to a chancre on the under aspect of the penis. A second lesion may appear on the inner aspect of the thigh from contact with one on the lateral surface of a labium majus, or from one on the penis. A second chancre in the



FIG. 13 Primary syphilis (Case 16)

pubic region may be shown to be in apposition to one on the penis when this organ is brought up against it.

Extragenital lesions are atypical more often than genital ones. Chancres of the finger may be accompanied by much pain. (Incidentally, most chancres of the finger occur in physicians, dentists, and nurses, and commonly appear at the edge of the finger nail.) Primary lesions of the lips may not show the typical hardness of the chancre, and may be associ-

ated with more edema, pain, and tenderness Cases 17, 18, 19, 20, and 21 present examples of extragenital chancres

Case 17. A twenty-seven year-old white male entered the Syphilis Clinic because of a "sore" on the tongue which had begun one month previously as a

FIG 14

FIG 15



FIG 14. Primary syphilis (Case 17)

FIG 15 Primary syphilis (Case 18)

'blister' The latter enlarged to a sore, and was accompanied by submaxillary swellings

Examination showed a generalized macular rash of which the patient was unaware Bilateral submaxillary lymphadenopathy was present A clean ulcer the size of a sixpence was present at the tip of the tongue On palpation it was found to be of cartilaginous hardness which involved the whole thickness of the tongue Blood Wassermann and Kahn tests were positive Unfortunately, darkfield examination was not carried out The lesion healed promptly under arsphenamine therapy

**Comment** This patient with an unrecognized rash in addition to an extragenital chancre bears out our belief that many patients with syphilis giving a negative history of the acute stage have probably overlooked some secondary manifestation (Figures 14 and 20)

Case 18. A twenty four year-old white male complained of a hard, painful 'fever blister' of ten days' duration

Examination revealed an indurated, crusted ulcer, 1 cm in diameter, on the upper lip The submaxillary lymph nodes were enlarged Serum from the lesion contained *T pallidum* Blood Wassermann and Kahn tests were positive

**Comment** This may be thought of as representing a fairly characteristic chancre of the lip (Figure 15)

Case 19 A sixty four year-old white man complained of two painful sores on the lips of five weeks' duration The lesions bled easily, there was an associated swelling in the neck

Examination showed the lesions to be hard, tender, and to bleed readily They were about 2 by 2.5 cm in size The left submaxillary gland was enlarged and

tender. Serum from the lesions contained numerous *T pallida*. Blood Wassermann and Kahn tests were positive.

**Comment** Multiple extragenital chancres are uncommon. A single lesion in a man of this age would suggest malignancy. The patient admitted kissing two neighbour children, aged seven and thirteen years. They had had a 'break ing out' six weeks before he kissed them. It was later learned through contact investigation that they had acute syphilis (Figure 16) (See Case 20).



FIG 16 Primary syphilis—multiple chancres (Case 19)

**Case 20** This sixty year-old white woman was brought to the Syphilis Clinic by her husband, the man in Case 19, because of a sore on her right breast. This had begun as a 'pimple' three weeks before, two months after her husband had developed the labial lesions, and one month after he was diagnosed as being syphilitic. They had not slept together after his diagnosis was established. She recalled having been awakened one night some six to eight weeks before by her husband either 'pinching or biting' her breast.

Examination showed below the areola of the right breast a firm, though not markedly indurated, crusted ulcer surrounded by an area of redness. There was no axillary lymphadenopathy. Darkfield examination of serum obtained from the lesion was positive for *T pallidum*. Blood Wassermann and Kahn tests were positive.

**Comment** The investigation of the small epidemic of syphilis opened up by the husband's case was of interest because of the several extragenital infections

This case represents an extragenital chancre derived from another extragenital primary lesion (Figure 17)

Case 21. A forty four year-old white married woman was known last to have a negative blood on February 1st at Vanderbilt University Hospital. On September 3rd she dressed a wild rabbit. Three days later the right index finger was tender, swollen, and presented an area that looked like "a burn"

FIG 17

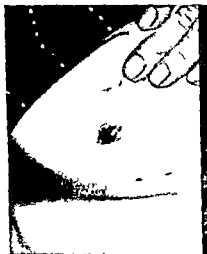


FIG 18



FIG 17 Primary syphilis (Case 20)

FIG 18 Primary syphilis (Case 21)

She opened it four days later but found no pus, two weeks later she developed axillary adenitis and the temperature rose to 103°

She visited the Surgical Clinic on September 25th where a granulating ulcer the size of a sixpence was described. Right epitrochlear and axillary nodes were enlarged and tender. The temperature was 100.4°. Agglutination test for *B. tularensis* was positive in a 1:40 dilution. Since routine blood Wassermann and Kahn tests were positive the patient was referred to the Syphilis Clinic on October 10th. Darkfield examination of material from the ulcer showed it to be swarming with *T. pallida*. At this time the lesion was soft, elevated, and bled easily. The blood agglutinated *B. tularensis* in a 1:320 dilution. After three injections of arsphenamine the lesion was completely healed. On October 24th agglutination tests were positive in a 1:40 dilution. The finger remained tender for a long time after healing.

**Comment** At the time the patient dressed the rabbit, a son had a genital chancre. She often handled his clothing. Did this patient have tularemia as well as a chancre? The rapid appearance, the high fever, and later increase in agglutinins suggest a tularemic chancre. The lesion then may have been contaminated with *T. pallidum*, with the development of a syphilitic chancre on the other. Incidentally, investigation of this family then revealed three acute



sequently, the syphilitic phase of a double infection may make itself manifest as in Case 11 )

On the basis of serologic reactions, syphilitic chancres are classed as either seronegative or seropositive. In the early days of the initial sore, the diagnosis can be established by darkfield examination only. This is the *stage of the seronegative primary sore*. It is immediately clear how great is the responsibility of the microscopist in assuming the burden of diagnosis in this stage. A positive diagnosis demands of the patient sixty or more weeks of treatment. Surely the darkfield diagnosis of syphilis is not to be undertaken lightly. Especially is this true in the case of oral lesions where there may be certain nonpathogenic organisms almost identical in appearance with the *T pallidum*. Anyone undertaking the darkfield diagnosis of syphilitic lesions must be willing to assume the grave responsibility of making a diagnosis without the assistance of serologic reactions for syphilis. Darkfield examination of primary lesions in expert hands yields positive results in a very high percentage of cases. Generally speaking, the organism of syphilis can be demonstrated with greater ease in chancres of short duration than in those of four weeks' or more duration. Of the 438 cases of primary syphilis of the genitalia in our series, the diagnosis was made in the seronegative stage in 156. *If the diagnosis of syphilis cannot be established by repeated darkfield examination, the clinician has no choice but to wait until such time as the blood tests become definitely positive, before treatment is instituted* (In our clinic it is the custom to follow patients who have suspicious genital lesions with blood tests twice a week for several weeks and then once a week until sixty days have passed since the appearance of the lesion )

A description of the satellite bubo or local lymphadenitis associated with the primary lesion appeared earlier in this chapter. This manifestation is commonly present, and has a diagnostic significance in primary syphilis. It also offers a possible source of material for darkfield examination if the sore has healed to such extent that *T pallidum* cannot be demonstrated in it.

**Case 22** A twenty-one year-old Negro became aware of a 'sore, tender spot' on his penis eight days previously. At the same time he noted a tender, small 'swelling' in the right groin, which had enlarged to the size of a walnut by the next day.

Examination revealed a large, tender, inguinal lymph node on the right. On the shaft of the penis was an indurated, crusted, and dry lesion 1.5 cm. in diameter. Since only one *T pallidum* could be found on darkfield examination, the lymph node was punctured and material obtained which contained many treponemata. Blood Wassermann and Kahn tests were positive.

**Comment.** The illustration shows the right inguinal adenopathy with the

site of the puncture. If all the clinical features of this case are taken into consideration, it seems certain that the lesion was of more than eight days' duration (Figure 19).

The value of the sentinel node also should be kept in mind in the presence of syphilitic infection without chancre, i.e. syphilis d'emblée.

With progress of the disease the serologic blood tests for syphilis become



FIG 19 Primary syphilis, satellite bubo (Case 22)

positive. This is the stage of the *seropositive primary sore*. Approximately one-half of the cases in the primary stage of syphilis will have developed a positive serologic test by the tenth to fourteenth day. Subsequent to this time the frequency of positive tests increases until by the end of the fourth week the positive reaction for syphilis has become established in almost all patients. Only rarely is the blood negative as late as the fifth or sixth week after the appearance of the sore. Over a period of some days to a week, between the negative and positive stages, the blood tests may give only a doubtful reaction because of the low reagin content in the blood. (See Chapter iv.)

#### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of syphilitic primary lesions involves a consideration of a number of conditions. The genital chancre must be differentiated from several nonsyphilitic diseases.

**Chancroid** This disease, due to the streptobacillus of Ducrey, probably is the most frequent lesion to be differentiated from the primary lesion of syphilis. It has an incubation period of only a few days, and appears as a red papule which rapidly breaks down to form an ulcer. (See Case 11.) The soft chancre, or chancroidal ulcer, typically is all that the hard chancre of syphilis is not. Thus the chancroidal lesion is a true ulcer with overhanging edges, presenting a base covered with dirty, grayish-white exudate, and bleeding very readily upon irritation as in the collection of serum for darkfield examination. The ulcer is very tender and painful so that the contact of clothing is uncomfortable. Because self inoculation of the skin readily occurs from infectious secretions of the original ulcer, multiple lesions are common. The sores spread and are destructive, often leaving deep scars or deformity of the glans due to loss of tissue. A common site of the chancroidal ulcer is at the frenum. The bubo commonly associated with a Ducrey bacillus infection progresses quite rapidly in a week or more to suppuration, and either drains spontaneously or may be incised. It may, however, resolve without suppuration. Following drainage, which persists for only a few days at most, healing is very prompt. It must be emphasized that occasionally the chancroidal lesion may closely simulate the syphilitic initial sore, and that the reverse may be true. The darkfield examination only can determine the presence of syphilis. The demonstration of the Ducrey bacillus is extremely difficult.

**Condyloma Accuminatum (Venereal Wart)** This common verrucous lesion of virus etiology associated with excessive secretions about the genitalia should offer little difficulty in diagnosis. These condylomata are commonly found on the glans, in the coronal sulcus, under the prepuce in the male, and about the vulva in the female. Occasionally they appear on the scrotum. The pink, cauliflower like growths vary in size from that of a pin head to that of a pea or even larger. Manipulation of the wart by the finger and the gristle like sensation noted upon scraping the growth with a scalpel immediately indicate that one is not dealing with a chancre.

**Granuloma Inguinale** Upon its first appearance as a firm nodule on or about the genitalia this disease may simulate the initial sore of syphilis. Its slow extension to contiguous skin areas, the granulomatous ulceration, and the contractile, depigmented scar in its later course distinguish this lesion from the chancre of syphilis. In its early stages when it may simulate syphilis, either darkfield examination for *T. pallidum* or the demonstration of Donovan bodies in the stained scrapings from the lesion may be necessary for diagnosis.

**Lymphopathia Venereum** The primary lesion of this disease may be that of an erosion or a papule lasting for several days. It appears within a few days after sexual exposure. Actually I have never found it to simu-

late the initial sore of syphilis except in the first few days of the latter. It offers a greater problem in diagnosis in secondary syphilis. The bubo in lymphopathia is painful, increases slowly in size, and consists usually of a mass of glands. The skin over it assumes a purplish red colour, becomes adherent to the mass, and eventually, in most instances, drains from several sinuses either spontaneously or by incision. Drainage often continues for months, and healing is followed by adherent multiple scars. The darkfield examination is the only means of establishing a diagnosis at the time the genital lesion may simulate a beginning primary sore of syphilis. Later the Frei test will help in the diagnosis of lymphopathia. With respect to the serodiagnosis it must be remembered that false-positive flocculation tests and anticomplementary complement-fixation tests occur at times in lymphopathia venereum.

**Carcinoma of the Penis.** The nodule of early carcinoma may occasionally present itself for differentiation from the syphilitic sore. Darkfield examination and serologic tests for syphilis must be employed depending upon the duration of the lesion in question. Carcinoma may occur in a patient who also has latent syphilis. Within the past year we have seen a patient with carcinoma of the penis and latent syphilis. He had had some months of antisyphilitic treatment for the penile lesion. Biopsy may be necessary to establish the diagnosis of cancer in an old man who presents a penile lesion with an indurated border. The practitioner who encounters an instance of cancer and positive blood tests for syphilis must realize that a lesion which does not heal after a couple of injections of an arsenical is probably not syphilitic.

**Fusospirochetal Infection.** The fusospirochetal organisms may be present about the genitalia in both sexes, and may act as secondary invaders in other lesions. Under such circumstances necrosis and gangrene of tissues may occur. Such secondary infection in the presence of chancreoid ulcer may lead to phagedenic gangrene of the genitalia.

**Gonorrhea.** There should be no difficulty in the differentiation of this disease from primary syphilis under ordinary circumstances. However, an intra-urethral chancre may be accompanied by a urethral discharge free of the gonococcus. Furthermore, in the presence of phimosis, balanitis may occur in either gonorrhea or primary syphilis. If palpation of the edematous prepuce reveals an infiltration suggestive of a chancre it should not be passed off as being of no significance. The examiner may be inclined to do so, especially if the gonococcus is found. We have found *T. pallidum* in addition to the gonococcus in the secretions in balanitis by the method of examination described in Chapter III.

**Lesions of the Uterine Cervix.** Primary lesions of the cervix may appear as erosions, ulcers, and diffuse infiltrations. Thus primary syphilis

must be thought of in the many conditions which occur in the cervix, including carcinoma. Since cervical disease is exceedingly common, it seems quite obvious that syphilis will not be considered seriously by the general practitioner or gynecologist unless he is dealing with a woman known to have been exposed to syphilis. My only experience with dark-field-positive lesions of the cervix uteri has been in patients already seropositive or with secondary lesions, so that I have never been certain as to the exact status of the cervical lesion, whether it represented primary or secondary syphilis.

**Scabies and Herpes Progenitalis.** These diseases more often offer problems in differentiation in secondary syphilis than in primary syphilis, and therefore will be considered in Chapter VII.

**Traumatic and Pyogenic Lesions.** Trauma, especially with secondary infection, and pyogenic infections occur about the genitalia and must at times be differentiated from primary syphilis. The history, appearance of the lesions, darkfield and serologic examinations must be used in the diagnosis.

**Other Syphilitic Manifestations.** The clinical characteristics of the darkfield-positive secondary lesions appearing on the genitalia—namely, moist erosions, papules, and condylomata lata—will be described in Chapter VII. Their differentiation from the primary lesion will be taken up at that time.

As a relapse phenomenon, a recurrent chancre or monorecidive may occur, and may simulate a primary sore even to an accompanying sentinel node. This lesion recurs at the site of the original chancre. Thus there should be a history of a previous sore, the blood tests for syphilis will be positive, and the darkfield examination will reveal *T. pallidum*. It is also probable that a history of inadequate therapy will be obtained in such a case.

Pseudochancres redux is the gummatous lesion which may appear at the site of primary infection many years before. Under such circumstances the history and a negative darkfield examination will be of assistance in the differentiation from an initial sore. Furthermore, the presence of other tertiary lesions if present will be of assistance in diagnosis.

Extragenital primary lesions offer greater difficulty in differential diagnosis merely because of the low index of suspicion found in the average physician. Any extragenital lesion which develops slowly and resolves slowly with a satellite bubo should be thought of as a possible syphilitic chancre.

**Lip.** Trauma usually offers no difficulty in diagnosis, although low-grade secondary infection may lead to a prolongation of its course and may account for an associated lymphadenopathy. However, trauma may offer

a portal of entry for *T pallidum*. One of our patients with a labial chancre had burned his lip with the lighted end of a cigarette while on a "petting party." The initial sore developed at the site of the burn. In a case seen with another physician, a young man had accidentally cut his lip in a friendly scuffle, a chancre developing at this site. Subsequently, it was learned that immediately after the injury he had drunk from a bottle after another man who was found to have had secondary syphilis at the time.

"FEVER BLISTER" is the complaint of the patient with a labial chancre, and too often the physician agrees with this. An indurated, slowly healing "fever blister" should always suggest the need for a darkfield examination and serologic tests for syphilis.

CARCINOMA OF THE LIP may be so closely simulated by primary syphilis that the diagnosis may be very difficult. The hardness, pearly edges, and accompanying adenopathy may suggest carcinoma. On the basis of the physical characteristics of a single lesion in Case 19 a diagnosis of carcinoma would have been logical, but in this case the multiplicity suggested disease other than newgrowth. Carcinoma of the lip may develop in the patient with seropositive latent syphilis. Failure of healing, after treatment, of a darkfield negative labial lesion in a person with a positive blood should indicate the necessity of a biopsy for diagnosis. This should be done soon after antisyphilitic treatment is begun, since a chancre would heal promptly.

TUBERCULOSIS OF THE LIP is practically never a diagnostic problem in so far as syphilis is concerned. The mucous membranes are rarely invaded by the tuberculous process until late in pulmonary disease, and then the manifestations will consist of multiple pharyngeal, palatal, lingual, and labial ulcers which are exquisitely painful.

**Tonsil.** Chancre of the tonsil may be difficult of diagnosis. A seronegative, darkfield positive tonsillar ulcer offers a clear-cut diagnosis of primary syphilis. Differentiation of a seropositive, darkfield positive tonsillar chancre from the mucous patch may be aided by the following points. The chancre is more infiltrated and may be accompanied by enlargement of the regional nodes, not as a part of generalized lymphadenopathy as would be the case in secondary syphilis. The duration of the tonsillar lesion before the onset of secondary manifestations also may provide a clue. Case 36 illustrates this problem. The comments made relative to tuberculosis of the lip apply to such disease of the tonsil. The differentiation from Vincent's angina and acute follicular tonsillitis depends mainly upon the more severe systemic reaction to these two conditions. Chills, high fever, leukocytosis, the evidence of local acute inflammation, and the great degree of pain and difficulty in swallowing accompanying acute non-syphilitic infections, usually make the true diagnosis fairly easy.

Evaluation of the results of darkfield examination in seronegative lesions about the mouth must be in the hands of one with much experience in this field because of the presence of nonpathogenic spirochetes which may closely resemble *T pallida*

**Other Extragenital Lesions** In pyogenic infections, tularemia, and paronychia, the chancre of syphilis may need to be considered in differential diagnosis. A slowly progressing and slowly healing indurated lesion should arouse a suspicion of syphilis. The darkfield examination and blood tests must be used to eliminate this possibility.

## PROPHYLAXIS

This subject will be discussed in the following chapter since the problem is the same in both the primary and secondary stages.

## TREATMENT

The continuous method of treatment is applicable to both primary and secondary syphilis, and therefore will be covered in Chapter VII.

Since the practitioner is frequently confronted with questions regarding local treatment in acute syphilis, a comment regarding this may be in order. The lesions of acute syphilis resolve so rapidly under adequate antisyphilitic treatment that local treatment is not at all necessary. It would seem best not to use any. Among illiterate and unintelligent patients, local therapy is likely to be given more credit than chemotherapy. For psychologic reasons it is wiser to promote credit for improvement to the injection of drugs. The chancre becomes darkfield negative within twenty-four to forty-eight hours after the first injection of an arsenical in adequate dosage. The lesion has usually practically disappeared within ten to fourteen days, during which time several injections of arsenic have been given.

## PROGNOSIS

As was indicated above, the uncomplicated primary lesion of syphilis heals spontaneously in a matter of from about two to six weeks in most instances. It may heal with or without a residual scar. In the evaluation of the prognosis under antisyphilitic treatment we must depend upon those sources which have had large groups of cases for study. We will need to use especially the figures published by the Co-operative Clinical Group. Since most of these statistics lump cases in the primary and secondary stages together, the prognosis of acute syphilis following treatment can best be discussed following a presentation of the subject of

secondary syphilis. Therefore certain information will be presented in the next chapter relative to the prognosis in primary syphilis.

### ADVICE TO THE PATIENT

Advice to the patient with respect to certain pertinent points is essential after the diagnosis of primary syphilis has been established. Since this applies to all syphilis in the infectious stage, this also will be covered in the next chapter.



## VII

### SECONDARY SYPHILIS

#### HISTORICAL NOTE

In the sixteenth century the cutaneous and mucosal lesions, as well as alopecia, were known to be part of early syphilis. It was known that extragenital infection could be transmitted by lesions which were probably secondary lesions. Innocent infection due to cupping, kissing, and the use of drinking utensils was described in the seventeenth century. In the nineteenth century Ricord, according to Pusey, established the primary, secondary, and tertiary stages of syphilis. He did not believe the secondary lesions to be infectious, but Wallace and Von Waller established this fact.

#### ONSET OF SECONDARY STAGE

It is a common belief that the stage of secondary syphilis represents the clinical manifestations of a widespread spirochetemia, and that as such it presents a definite sequence to the primary stage. Actually, such is not the case. It is difficult to say when the primary stage ends and the secondary is ushered in. We know that a spirochetemia is present very early in the primary stage. Raiziss has shown in rabbits that when the *T pallidum* is inoculated into the testicle it appears in the blood stream very promptly, even in a matter of minutes. Such inoculation results in the rabbit cannot necessarily be translated into a similar course of events in the naturally infected human host. (The instrumentation attendant to inoculation may account for organisms in the blood stream.) There is sufficient clinical evidence to indicate a spirochetemia in the seronegative primary stage of syphilis, however. The best evidence is the fact that recipients of blood from transfusion donors in the seronegative primary stage have become infected. Furthermore, objective evidence of central-nervous-system invasion may be demonstrable in the primary, seronegative phase of syphilis.

It is generally stated that the secondary stage begins in from six to eight weeks after the appearance of the chancre. The time, however, is extremely variable. Not uncommonly secondary manifestations are present when the history indicates that the primary lesion is of three or four weeks' duration, and at a time when the chancre is still active with many treponemata demonstrable upon darkfield examination. Again, the chancre may have healed, and some weeks or months may have passed before the secondary symptoms and signs make themselves manifest (delayed secondary syphilis). The following figures are of interest in the over-

lapping of the primary and secondary stages of syphilis. Since, on our records, the diagnosis recorded is that of the stage in which the patient was admitted, residual chancres in the presence of a secondary rash probably were more frequent than indicated. Among 857 cases of cutaneous secondary syphilis, the chancre was still present as shown below:

Negro males	—262 cases, chancre present in 63 (24%)
Negro females	—241 cases, chancre present in 12 (4.9%)
White males	—172 cases, chancre present in 56 (32.5%)
White females	—182 cases, chancre present in 34 (18.6%)

In syphilis d'emblee (syphilis without chancre), the secondary manifestations may present the first evidence of the syphilitic infection.

Statistical studies show that when patients are confronted with the serologic or clinical evidence of syphilis later in life, only 50 to 60 per cent can recall manifestations suggestive of the secondary stage of syphilis. Thus it is probable that a fair percentage of patients have had no clinical evidence of the systemic invasion. However, I question this apparent lack of acute syphilis in 40 to 50 per cent of patients. It seems probable that lesions of secondary syphilis had been present, but were too evanescent or minor to be noted. Not uncommonly in our clinic we see patients referred from other clinics in the hospital because of a positive blood test for syphilis, and upon careful scrutiny we find secondary lesions of which the patient was unaware. The same is true among contacts of acute cases. Obviously the patient may be unaware of a small moist erosion at the anus, a mucous patch in the mouth, or a faint macular eruption. It is very likely that such lesions are overlooked by the patient, and as a result in later years he cannot recall having had any of the mucocutaneous lesions of secondary syphilis.

#### PATHOLOGY

The basic pathology is the same as that of the chancre. Although clinically one speaks of macules and papules, pathologically the only difference between the two types of lesions is the amount of inflammatory infiltrate, the vascular damage, and the resulting epidermal changes secondary to the process. The walls of the capillaries are thickened, and there is an extensive round-cell infiltration about them. Due to the cellular infiltration, the papillae may be flattened out. In papules there is a widespread infiltration of lymphocytes and plasma cells in the corium. There is a slight connective tissue increase in the healing papules. The follicular lesions show some infiltration deep about the hair follicles, with demonstrable treponemata.

The moist lesions, mucous patches, erosions, and condylomata, starting as papules, take different forms because of their sites. Here there is a

productive inflammation in the papillary layers. The papillae enlarge, and the epithelium is swollen. Necrosis and exfoliation of the epithelium occur, producing the mucous patches in the mucous membranes, and the erosions about the genitalia or moist areas of the skin. Similarly, the condyloma latum presents swelling of the papillae, and thickening and exfoliation of the epithelium. These lesions with epidermal proliferation are swarming with the organisms of syphilis. The submucosa, as in the case of the skin, has the characteristic capillary and pericapillary changes. With respect to the pathogenesis of the pathologic change in the skin, I quote Michelson as follows: "We do not know whether the spirochetes were deposited before the appearance of the exanthem and awaited a rise in tissue allergy to make their response, whether they suddenly left the circulation at the end of the so-called secondary incubation period and penetrated the skin in great numbers and incited the already allergic skin to eruption, or whether the eruption may have been caused entirely by liberated toxins. Deep excisions made from apparently uninvolved areas of the skin during the height of eruption have revealed perivascular foci of infiltrate, strengthening the view that the eruption is an inflammatory reaction against invasion."

The lymph nodes show proliferation of endothelial cells and perivascular collections of round cells.

## CLINICAL MANIFESTATIONS

### SEROLOGY

Diagnosis by serologic methods fortunately is of great assistance in the secondary stage of syphilis. By the time this stage has been reached, the complement fixation and precipitation tests are positive in all cases. Personally, I have yet to see a patient with secondary syphilis in whom the serologic tests for syphilis are negative. The Co-operative Clinical Group has stated that a small percentage of cases in this stage are seronegative, but the figures may be questioned. Some of the cases in the Co-operative Clinical Group studies go back to years when antigens and techniques of blood tests lacked the present-day reliability. One also suspects that some of the cases of decades ago were diagnosed clinically alone, and obviously even the best clinician is not infallible in his diagnosis. Furthermore, it is unfortunate that the studies have not indicated whether one or more blood tests were done in those cases reported as being serologically negative. In our experience the first blood specimen in a patient with fully developed secondary syphilis may have been reported as negative, and subsequent ones taken within a few days as strongly positive. This has only one meaning, namely, an error. Therefore, on the presumption that the laboratory can be trusted, no physician is justified in making the diagnosis of secondary syphilis in the face of negative serologic tests.

## CONSTITUTIONAL SYMPTOMS

Preceding the appearance of the secondary eruption the patient may experience the manifestations of generalized infection as in any infectious disease. The absence or presence, and degree of such symptoms is extremely variable and, as in other infections, probably depends upon the host's reaction to infection. The symptoms often become intensified at the time of the eruption, if such occurs.

Some fever is common, varying from elevations of one-half of a degree or two and uncommonly three degrees or more. It is usually intermittent. Malaise and mental depression are common. Anorexia may occur, occasionally nausea. Weight loss is frequent. Sore throat is often present. Headache and aching referred to the bones, joints, and muscles is very frequent. Secondary anaemia may occur, and a moderate leucocytosis with a relative lymphocytosis is common.

## DERMATOLOGIC LESIONS

**Cutaneous Lesions** The day has passed when the diagnosis of secondary syphilis was made on the basis of a detailed consideration of dermatologic manifestations. At the present time a diagnosis of secondary syphilis without confirmation by darkfield examination or positive blood

TABLE VIII

DISTRIBUTION OF SECONDARY SYPHILIDS BY TYPE, RACE, AND SEX

Type of Rash	Incidence per cent of Total	Negro		White		Total
		Male	Female	Male	Female	
Macular	32.9	92	59	63	68	282
Maculopapular	36.3	80	86	67	80	313
Papular	19.2	56	53	33	23	165
Circinate (annular)	6.8	24	27	2	5	58
Pustular	1.9	5	5	4	3	17
Follicular	0.7	—	7	—	—	7
Pigmentary	0.7	2	4	—	—	6
Psoriasisiform	0.3	—	—	2	2	4
Rupial	0.4	3	—	1	—	4
Ulcerative	0.1	—	—	—	1	1
Totals	100.0	262	241	172	182	857

tests for syphilis cannot be justified. Nevertheless, some consideration must be given to the mucocutaneous lesions of this stage of syphilis in

order that they may be recognized for what they are, and to differentiate them from other common skin diseases. Obviously, the purposes of this book restrict the considerations to the more common of the syphilitic lesions.

The skin lesions consist basically of macules and papules, rarely pustules. A combination of these may occur to provide numerous patterns. Vesicles



FIG 20 Secondary syphilis—roseola (Case 17)

do not occur in acquired syphilis. As is to be expected with wide dissemination of the organisms, the lesions may be general in distribution, are usually multiple, and tend to appear in successive crops. Thus skin lesions of varying age may be seen at the same time—polymorphism. The individual lesions are infiltrative and discrete, but have a tendency to be grouped in patches or clumps. Skin lesions of secondary syphilis tend toward chronicity in their course, are mild, without suppuration or scarring, and, with one exception (follicular syphilid), do not itch to any extent. Residual pigmentation and depigmentation rarely occur. In the past much has been made of the colour of syphilids, but because of their variability, colour is not worthy of much emphasis. The colour is frequently brownish-

red, but numerous tints may be encountered. The dry skin lesions of syphilis are noninfectious unless deep layers are laid open. The moist eroded ones are infectious.

The distribution of the secondary cutaneous lesions in 857 cases at the Vanderbilt University Hospital Syphilis Clinic as to type, race, and sex is presented in Table VIII.

**MACULAR RASH (ROSEOLA)** This eruption presents itself as a generalized, faint pink roseola (Figure 20—Case 17). The macules are usually from about 0.5 to 1 cm. in diameter—at times larger—and are seen at their best over the back, chest, abdomen, and arms. In its faintest form, the rash may easily be missed in a poor or artificial light. It can, at times, be best discovered by inspection from a distance of several feet. Not infrequently, upon the demonstration of a patient with a faint roseola to a group of students, some do not see it and have to move about until the light strikes the patient at a proper angle to make it visible. Often when the patient's attention is called to the rash, he expresses surprise at its presence. In the coloured race the rash must be quite red to be visible in the mulatto, and I suspect has been missed time and again in the pure Negro. At times one suspects the presence of a macular rash, but cannot be certain about it. With proper illumination the maculae may be seen to be somewhat edematous and slightly elevated.

**PAPULAR SYPHILIDS** Often the macular eruption shades into a papular one, and thus the term maculopapular rash is often pertinent. However, the eruption of secondary syphilis may be purely papular. The distribution of such lesions is the same as that of the macules, but in addition there is commonly a tendency for the papules to appear on the palms and soles. Papules are definitely infiltrative lesions, and on the palms and soles especially they may actually feel shotty. Palpation of the papules clearly indicates that the deeper layers of the skin are infiltrated by the inflammatory process. In contrast to the roseola, the papules usually have a brownish tint in addition to the basic red colour. They may vary in size from several millimeters to a centimeter or more in diameter, they are rounded or flat. The surface may be smooth or may present a slight collarette scale in the late stages. At times they actually have crusts. Cases 23, 24, and 25 present examples of papular syphilids.

**Case 23** A twenty three year-old white housewife entered the Syphilis Clinic because of a rash of one week's duration. This was noted first on the palms, and became generalized in the succeeding week. She had noted a sore throat. Her husband had gonorrhea at the time.

Examination revealed indurated, pink papules on palms and soles. Over the trunk, arms, and hairline of the scalp was found a macular eruption, which in

places was beginning to be papular Blood Wassermann and Kahn tests were positive

**Comment** The patient presented a maculopapular eruption The coloured reproduction (Frontispiece) illustrates the distribution and colour of the rash as it appeared on the forearms and palms

**Case 24** A twenty-eight year old white man was admitted to the Syphilis

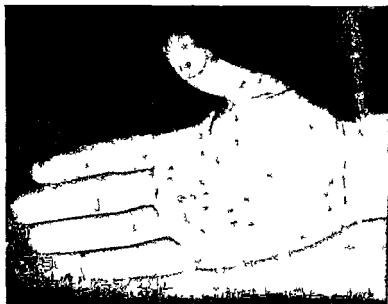


FIG 21 Secondary syphilis—papular rash (Case 24)

Clinic because of a "breaking out on the hands and feet" Two weeks before he noted malaise, sore throat, swollen glands behind the ears, and an eruption on the hands and feet There had been no chancre, but a bilateral inguinal adenopathy appeared one week before the development of the above symptoms His blood was known to have been negative a year before, but was found to be positive at the time of the appearance of the rash The last admitted extra marital sex exposure had been about five months before admission to the clinic.

Examination revealed a very faint macular eruption upon the trunk The palms and soles were heavily seeded with reddish brown papules which felt shotty Mucous patches were present on the hard palate There was a generalized lymphadenopathy Blood Wassermann and Kahn tests were positive The *T pallidum* was found in material from the mucous patches

**Comment** Figure 21 offers a good example of the papular eruption found upon the palms and soles, so characteristic of secondary syphilis In addition there was a roseola on the trunk There was no history or evidence of a chancre

**Case 25** An eighteen year-old white married man developed a painless

penile sore three months before. Three weeks later more lesions appeared on the genitalia and in the groin, those on the face appeared one month before admission.

Examination disclosed papules present on the forehead, bridge of the nose, the chin, at the nostrils, on the scalp, and at the umbilicus. These were brown in colour, flat, and infiltrated. Numerous crusted papules were present on the

FIG 22

FIG 23

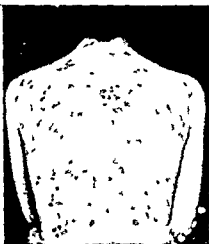


FIG 22 Secondary syphilis—papular rash (Case 25)

FIG 23 Secondary syphilis—psoriasiform rash (Case 26)

penis, scrotum and thighs. A moist flat papule was found at the anus. The prepuce was so swollen it could not be retracted. There was a generalized lymphadenopathy. Darkfield examination of material from a papule on the scrotum revealed the *T. pallidum*. Blood Wassermann and Kahn tests were positive.

**Comment** The papular type of lesion shown in this case is one seen more often later in the secondary stage than indicated in this history (Figure 22).

In addition to the pure papular type just described there are several variations which, because of their characteristics, have warranted certain descriptive names.

**PSORIASIFORM SYPHILID** Occasionally in the case of a maculopapular rash the papules may become larger plaque-like lesions which may be several centimeters in diameter. They are infiltrated, dark-red in colour, and are covered by scales, which are either thin and brush off easily, or thick and adherent. In this scaling papular syphilid there may be mild itching.

**Case 26** A twenty-one-year-old white married woman was referred to the Syphilis Clinic because of a skin rash of three weeks' duration.



Examination revealed a widespread papular eruption involving the lower half of the face, the chest, back, and abdomen. The papules were red and covered by a moderately thick, white scale which was easily removed, leaving a dry surface. The largest lesions were 2.5 cm in diameter. A few papules were found on the palms, there were numerous nonscaling papules in the groins. The external genitalia were swollen and red, but presented no syphilids. Material obtained from the papules in the groin contained *T. pallidum*. Blood Wassermann and Kahn tests were positive.

**Comment** The psoriasisiform secondary rash is rather uncommon. Contact investigation revealed seropositive primary syphilis in the husband and a history indicating that he had been infected but recently (Figure 23).

**FOLLICULAR SYPHILID (MILIARY PAPULE)** This type of eruption consists of pinhead size, pointed papules involving the hair follicles, and may be accompanied by intense itching. Although the distribution may be general, the lesions are most commonly found on the back, chest, arms, and thighs. Characteristically the follicular lesions tend to appear in groups, as is well illustrated in Case 27. Extensive scaling is seen at times as is shown in Case 28. The follicular type of eruption occurs almost exclusively in the coloured race. Because of the lack of hair follicles, palms and soles are not involved. Follicular syphilis of the scalp is accompanied by alopecia.

**Case 27** A twenty four year-old Negress complained of a generalized rash of eight days' duration. Itching was intense and constant.

Examination revealed a rash consisting of pinhead sized papules, of a follicular distribution over the face, back, chest, abdomen, and extremities. They were of a purplish colour, and arranged in groups. None was found on the palms, soles, or genitalia. Blood Wassermann and Kahn tests were positive.

**Comment** This is a characteristic example of the so-called follicular secondary rash seen in the coloured race. Response to treatment was prompt (Figure 24).

**Case 28** A twenty-one year-old Negress, known to be seronegative ten months previously, was referred to the Syphilis Clinic because of a rash of eight days' duration. Some weeks before the appearance of the rash, she had had a 'boil' on the thigh.

On examination a papular rash was found upon the arms, trunk, thighs, and at the nape. Material from the papules was darkfield negative, and therefore a blood sample was taken. The patient failed to return for ten days. During this time the skin lesions had increased markedly in number and were now definitely follicular in distribution. Thick white scales were prominent. Blood Wassermann and Kahn tests were positive.

**Comment** This is an example of excessive scale formation in a follicular syphilid. Involution of the lesions began promptly after one injection each of

old arsphenamine and bismuth salicylate, with loss of the scaliness in one week (Figure 25).

**LENTICULAR PAPULAR SYPHILID.** These are papular lesions, tending to appear in clumps. The individual lesion presents a shiny surface, at times with a thin scale, and varying in size from a pea to a bean.

**PUSTULAR SYPHILID.** A pustular rash in secondary syphilis is rare and

FIG 24

FIG. 25

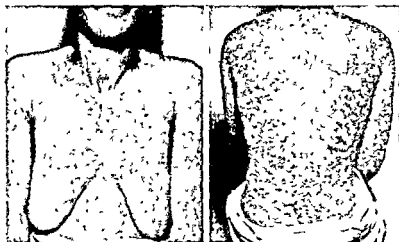


FIG 24. Secondary syphilis—follicular rash (Case 27).

FIG. 25. Secondary syphilis—follicular rash (Case 28).

found more often in the Negro than in the white race. The lesions usually occur on the scalp or on the face (Case 29). Such lesions do not present the active inflammatory appearance of a pyogenic pustule, but usually appear to be merely a softening or breaking-down in a papule. Upon removal of the crust, an umbilicated lesion with a moist centre is found. (A similar lesion may appear as a Herxheimer reaction in a papular eruption in which pustulation occurs within twenty-four hours after administration of an arsenical.) With a widespread distribution of pustules the clinical picture may suggest *variola*. A very rare form of pustular syphilid is that associated with more extensive indolent ulceration covered by thick rough stratified crusts. This is the so-called **RUPIAL SYPHILID**.

**Case 29.** An eighteen-year-old Negress entered the Syphilis Clinic because of a skin eruption of ten days' duration.

Examination revealed many crusted papules, some of which were pustular, distributed over the face, scalp, and back of the neck. They had become confluent in places. The rest of the skin was free of lesions except for two crusted papules on an arm and thigh. Two kissing condylomata lata were present on

the labia minora *T pallida* were demonstrated in these Blood Wassermann and Kahn tests were positive

**Comment** A diagnosis of pyogenic infection might easily have been made in this patient The condylomata gave the clue to syphilis Three injections of an arsenical in ten days completely healed the lesions leaving only residual pigmentation (Figure 26)

FIG 26

FIG 27



FIG 26 Secondary syphilis—pustular rash (Case 29)

FIG 27 Secondary syphilis—annular syphilid (Case 30)

**MALIGNANT SYPHILIS** Of extreme rarity is the so called malignant form of secondary syphilis In this type, papular secondary lesions become pustular, and produce deep ulcers associated with tissue destruction Healing occurs with scar formation Only one such instance has been met with in our 857 cases of secondary syphilis In this case the ulcerative process laid bare the subcutaneous tissues at various sites on the face, trunk and extremities Fever and toxemia accompanied the process Of interest in this case was the necrotizing primary lesion, and the long interval before the serologic tests were positive The whole clinical course in such a case suggests some deficiency in the host's immune mechanism

**CORYMBOSE SYPHILIDS** This term merely calls attention to a special grouping of papules A central larger papule is surrounded by a number of smaller ones

**ANNULAR SYPHILIDS** The lesions of secondary syphilis may appear as papules which spread at the periphery and involute at the centre In Cases 30 and 31 there is an excellent history of such progression The border of such a ring like lesion is infiltrated reddish brown in colour, and may consist of small discrete papules or may appear as a continuous zone of induration

Case 30. A twenty-nine-year-old white housewife was referred from the Gynecology Clinic, where she had been seronegative five months previously. A genital sore was denied. Three months before this admission red papules appeared on the arms and ankles. They remained unchanged for nine weeks, when they began to enlarge to a size from a sixpence to a shilling. The centres then cleared, leaving ring-shaped lesions. Similar ones appeared on the palms and soles.



FIG 28. Secondary syphilis—annular syphilid (Case 31).

Examination revealed many papules and some annular lesions on the forearms, hands, palms, legs, dorsum of feet, and soles. There was one annular lesion on the face. Clusters of papules were grouped over the shoulders. The skin in the centre of the annular lesions was normal. Blood Wassermann and Kahn tests were positive.

*Comment.* The annular rash is a rather uncommon syphilitic manifestation in a white person (Figure 27).

Case 31. A twenty-one-year-old Negress entered the clinic because of a "breaking out" of three months' duration. The lesions each began as a "pimple" which spread to assume the form shown in Figure 28. Her husband began to take "shots" about four to six weeks before the appearance of the rash.

Examination revealed a maculo-papular rash upon the forearms and back. On the thighs were found lesions having annular or serpiginous outlines. The borders were raised and dull red in colour. There was generalized glandular enlargement. Blood Wassermann and Kahn tests were positive (Figure 28).

Annular (circinate) lesions may appear as perfect rings. This is especially true in Negroes among whom such lesions are at times called "money spots." The pattern may be circular or polycyclic. Case 32 illustrates both forms, the perfectly circular ones on the forehead, and the polycyclic one at the angle of the mouth. The borders of these circinate lesions are elevated and pinkish in colour, the centre often is more darkly pigmented than the normal skin. The favourite sites of the circinate lesion in the Negro are the face—especially about the nose, mouth, and chin—the back of the neck, the back, shoulders, wrists, and buttocks. In Negro males the annular lesions may appear on the scrotum and shaft of the penis. Except in Negroes, annular lesions are relatively rare in secondary syphilis. This type of skin reaction is more commonly seen in white persons with secondary relapse.

**Case 32.** An eighteen-year-old Negro was placed on antisyphilitic treatment elsewhere two months previously, because of a penile lesion and a positive blood test. In spite of this an eruption appeared on the face.

Examination showed circinate lesions on the face and neck. The borders were elevated and pink in colour. A condyloma was present between the thigh and scrotum. Serum obtained from the condyloma contained *T pallidum*. Blood Wassermann and Kahn tests were positive.

**Comment.** This patient complained of progressing skin lesions in spite of treatment. Though the dosage was not known, it may have been inadequate, for arsphenamine in the usual dosage caused immediate clearing of the rash (Figure 29).

**LEUKODERMA COLLI.** The "collar of Venus" is an unusual residuum following a macular syphiloderm, appearing most frequently in brunette women. This may be encountered in Negroes. It consists of a series of depigmented spots, from 2 or 3 mm up to 1 cm in diameter, characteristically located about the neck and shoulders. They last for months and even years, and are unaffected by treatment.

**PIGMENTARY LESIONS.** In Negroes papular or circinate lesions may rarely leave markedly pigmented areas. At such sites the skin may be very thin and atrophic.

**Case 33.** A twenty-two-year-old Negress was known to be seronegative fourteen months previously. The last sexual exposure was given as four months before admission. A month later she noted a rash on the face, trunk, and extremities, which cleared after six weeks, leaving "black spots" at the site of former lesions. At the time the rash appeared she noted a fissure between the toes which enlarged and bled easily. Her blood was found to be positive at the same time.

Examination revealed a widespread distribution of pigmented, depressed atrophic scars on all parts of the body except the abdomen. They were 0.5-5 cm.

in diameter. There was generalized lymphadenopathy. Condylomata lata were found on the genitalia and at the anus, and a nontender ulcer with raised edges was present between the toes. Material from the condylomata and the foot ulcer showed *T. pallidum*. Blood Wassermann and Kahn tests were positive.



Fig. 29 Secondary syphilis—circinate syphilid (Case 32)

**Comment.** The moist lesions responded rapidly to treatment. The pigmented skin lesions were persistent for at least three years. This also provides an example of the condyloma latum between toes (Figure 30).

**ALOPECIA**, in secondary syphilis, occurs as the result of a follicular involvement and may be the only obvious cutaneous lesion. It most often involves the scalp, but eyebrows and eyelashes may be lost. Other parts

of the body may be affected in the process. The characteristic hair loss is patchy, so that the term *moth eaten* is used to describe it (Case 34)



FIG. 30 Secondary syphilis—pigmentary syphilid and condyloma latum (Case 33)

Usually the condition is temporary with restoration of the normal hair distribution some months later. Wile has shown that hair loss in the secondary stage may be neurogenic. He believes the hair loss in meningeal syphilis is due to involvement of the autonomic nervous system.

**Case 34** A twenty-one-year-old Negro complained of "falling hair." He was known to be seronegative six months before. Two months before admission he had a penile lesion, a month later he noted a rash, and his hair began to fall out.

Examination revealed a "moth eaten" pattern of alopecia of the scalp. Eye-

Fig 31

Fig 32

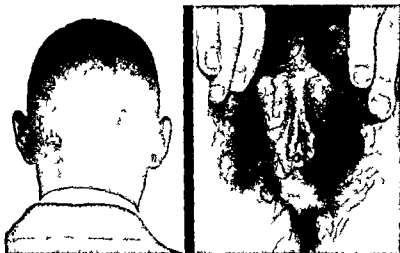


FIG 31 Secondary syphilis—alopecia (Case 34)

FIG 32 Secondary syphilis—condyloma latum (Case 35)

brows and eyelashes were gone. There was a generalized lymphadenopathy. Blood Wassermann and Kahn tests were positive.

**Comment** The type of alopecia was typically that of syphilis, and complete restoration occurred under treatment (Figure 31).

**CONDYLOMA LATUM** This moist lesion constitutes the most infectious manifestation of syphilis if measured in the number of treponemata per cu mm. of serum (See Chapter 11.) It is one of the most frequent manifestations of acute syphilis, especially in the Negro. Often it is the only sign of the disease. The lesion presents itself as a flat raised plaque varying from several millimeters to several centimeters in diameter. It is grayish white in colour, and usually has a smooth surface which is moist and covered with a slight gray exudate. Unlike the condyloma acuminatum (venereal wart), the condyloma latum is not pedunculated and does not have overhanging edges (Case 37 is an exception to the latter).

These vegetative lesions occur as the result of irritation, uncleanness, moisture, and warmth, and therefore are found especially in folds of the skin. Such predisposing conditions especially account for the high frequency of these lesions about the vulva, and in the perineal and anal



regions of both sexes. Less often they are found on the scrotum, in the groin, on the inner aspect of the thighs, at the umbilicus, between the toes, under pendulous breasts, in the axillae, and in the deep nasolabial folds of the Negro. We have seen the condyloma latum back of the ear (Cases 33, 35, 36, 37, and 38)

FIG 33

FIG 34

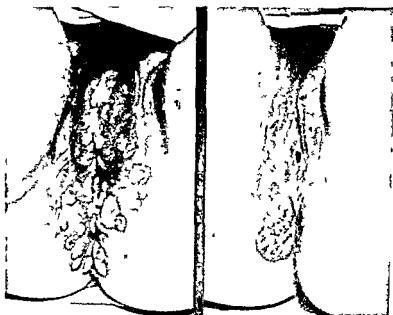


FIG 33 Secondary syphilis—condyloma latum (Case 36)

FIG 34 Secondary syphilis—condyloma latum (Case 37)

**Case 35.** A twenty-year-old unmarried white female complained of a severe sore throat of one month's duration. Enlargement of the left submaxillary nodes had been noted. She was aware of genital lesions for a period of three weeks.

Examination revealed the tonsils covered with a gray exudate. Enlargement of the left submaxillary and left inguinal nodes was present. Each labium majus, on its inner aspect, showed an elongated, flat, ribbon-like condyloma. Darkfield examination of serum from the condylomata showed *T. pallidum*. Blood Wassermann and Kahn tests were positive.

**Comment.** The condylomata in this case might easily have been overlooked since they were only visible on separation of the labia (Figure 32).

**Case 36.** A nineteen-year-old white widow complained of genital lesions of one week's duration, and an ulcer of the lower lip two days before this.

Examination revealed an elevated, plaque-like white lesion the size of a six-pence on the right anterior tonsillar pillar. Mucous patches were present on the

left tonsil and the lower lip. Only the right submaxillary glands were enlarged. A red, macular rash was present on the back and abdomen, brown, scaling, maculopapular lesions were present on the palms and soles. Moist papules were present under the breasts and in one axilla, and a large moist eroded area was found under the right second and third toes. Numerous condylomata covered the vulva and perianal region. Darkfield examination of serum from condylomata and from the moist lesion under the toes showed many treponemata.

**Comment.** This patient gave the names of four contacts. She had kissed two and had had sexual intercourse with the other two. The appearance of the lesion of the right tonsil, and its sentinel lymphadenitis, suggested very strongly that this represented a chancre of the tonsil. This patient presented many secondary manifestations (Figure 33).

**Case 37.** A fifteen year-old Negress entered the clinic because of a genital "sore." A hard, nontender sore appeared on the left labium majus three months before and disappeared in one month. This was followed immediately by the lesion which brought her to the clinic.

Examination disclosed a white scar on the left labium majus at the level of the vaginal orifice (shown in the photograph). To the right of the anus was a soft, granulomatous mass 2 by 3 cm in diameter, with overhanging edges. Darkfield examination of material from the tumour showed *T pallidum*. Blood Wassermann and Kahn tests were positive.

**Comment.** This condyloma latum is atypical in its granulomatous appearance and overhanging edges. It constituted the only secondary manifestation in this patient (Fig. 34).

**Case 38.** An eighteen-year-old Negress complained of genital "sores" of a week's duration. Several days later she noted a rash on the arms and in the axillae.

Examination showed a maculopapular eruption on the arms, trunk, and thighs. Several circinate lesions were found on the neck and shoulders. Condylomata were found in each axilla, on the vulva, and in the perianal region. *T pallida* were demonstrated in the condylomata. Blood Wassermann and Kahn tests were positive.

**Comment.** Several forms of secondary syphilis were present in this patient. It presents an example of the highly infectious condylomata lata in the axillae (Figure 35).

**Mucous Erosions of Secondary Syphilis.** **MUCOUS PATCHES.** The mucous-membrane manifestations of secondary syphilis correspond to the maculopapular syphilid. The erosions appear on the lips, gums (at times between the teeth), under the tongue, buccal mucosa, on the hard and soft palate, uvula, tonsils, and posterior pharyngeal wall. In these sites the lesion may appear first as a slightly elevated round or oval area, with little inflammatory reaction about it. The surface may present a gray membrane, unless it has been wiped off. If the surface has been removed, the lesion appears as an erosion with a clean base or with a grayish-white membrane.

Usually there is little associated pain or discomfort. The usual size of the mucous patch is of a diameter of several millimeters up to a centimeter or more. At times the lesions become confluent, and may present irregular borders, again, they may ulcerate deeply, especially in the case of tonsillar involvement. On the dorsum of the tongue the mucous patch is unlikely to present itself as an erosion, but rather as a bald pinkish patch. At the

FIG 35

FIG 36

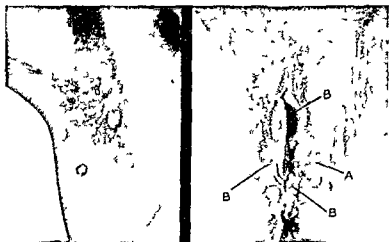


FIG 35 Secondary syphilis—condyloma latum (Case 38)

FIG 36 Secondary syphilis—moist erosions (Case 39)

mucocutaneous junctions, as at the angles of the mouth, moist papules appear covered by a gray membrane, or, if eroded, as fissures. Mucosal lesions of the mouth contain many *T pallida*, which lie quite superficially because of the moist character of the lesions. Therefore they probably account for the greatest number of nonsexual syphilitic infections. Kissing and the common use of drinking utensils, gum, and any other fomites used in the mouth contribute to the acquisition of innocent infections. (Since the mucous patches of secondary syphilis and those of secondary relapse are identical, Cases 50 and 51 in the following chapter may be considered as examples of these lesions.)

**MOIST EROSIONS OF THE GENITALIA** Moist lesions are very common on the mucous membranes and thin skin of the genitalia, and are the equivalent of maculopapular lesions. Because moisture, irritation, and uncleanness are factors in their production, they occur especially on the vulva and under the prepuce in the male. Usually these moist lesions are oval or circular and of several millimeters in diameter, and may or may not be covered by a membrane. At times they reach such size that one moist

erosion may, for example, involve the whole inner aspect of the labium minor, or the whole glans penis in the presence of a redundant or phimotic prepuce

In the female, moist erosions commonly appear about the vulva on or between the labia majora and labia minora, on the clitoris, at the urethral meatus or introitus. They may appear on the cervix, or the whole cervix may present such a widespread manifestation (Case 39). In the male, moist erosions occur at the corona of the glans, on the glans and the inner surface of the prepuce (Case 40). In the case of a tight foreskin, fissures frequently are seen to form a rosette at the edge of the nonretractable prepuce, these represent moist lesions of syphilis. Moist erosions also may occur on the skin of the scrotum, and especially on the inferior aspect of the penis at its base where it is in contact with the scrotum. In both sexes moist erosions occur at the mucocutaneous junction of the anus, between the folds of the anal mucosa and on the surface of hemorrhoids. Moist lesions may occur between and under the toes (Case 36).

**Case 39** A nineteen year-old white girl entered the clinic through contact in vestigation. Three weeks before she noted a pimple between the left labium and thigh. This enlarged to the size of a sixpence. Two weeks later several itching lesions appeared on the genitalia.

Examination revealed an indurated, crusted lesion (A), the size of a threepence, between the left labium majus and the thigh. (This is hidden by the hair.) The labia minora were swollen and on their surfaces were several moist erosions (B) 2-6 mm in diameter. Similar lesions were found at the anus. The anterior lip of the cervix uteri presented an erosion. Darkfield examination of material from the erosions on the labia minora and the cervix uteri swarmed with *T pallida*. Blood Wassermann and Kahn tests were positive.

**Comment** This patient presented the residual chancre, as well as secondary moist lesions. She demonstrates well that *T pallidum* can be found on the uterine cervix (Figure 36).

**Case 40** A twenty-eight year-old white married man complained of an eruption. Six weeks before the patient noted a sore throat which gradually improved. Marked weakness forced him to bed, and he lost nineteen pounds. A month before admission he noted lesions on the scalp, at the nares, and on the penis. A left inguinal node was enlarged.

Examination showed a few crusted papules on the scalp and mucous patches on the tonsils and their pillars. A nonindurated, dirty ulcer was present on the shaft of the penis. Moist papules and erosions were present on the glans, prepuce, and scrotum. An indurated, cord like structure ran the length of the penis on the inferior aspect. The skin was red over this. There was generalized lymphadenopathy. Material from genital lesions was positive for *T pallidum*. Blood Wassermann and Kahn tests were positive.

**Comment** The moist papules and erosions of the glans are well shown in the

photograph The position assumed by the penis on being lifted indicates the induration associated with the lymphangitis on its inferior aspect Contact investigation revealed secondary syphilis in the wife (Figure 37)

The moist erosions of the genitalia come and go, and are nonpainful Usually the patient is unaware of their presence Wiping such lesions with gauze or a cotton pledget will cause enough oozing of serum for the



FIG 37 Secondary syphilis—moist erosions and lymphangitis (Case 40)

demonstration of the numerous *T pallida* which are always present Certainly the friction of intercourse will do the same, and this indicates the rôle these apparently benign and frequently missed lesions play in the transmission of syphilis

**Differential Diagnosis of the Mucocutaneous Lesions of Secondary Syphilis.** The diagnosis of some of the mucocutaneous lesions of secondary syphilis may offer difficulties at times The practitioner must establish the diagnosis of secondary syphilis through verification by a laboratory examination—either the darkfield examination or a positive blood test It is important, however, to point out that a positive blood test does not necessarily mean that the mucocutaneous lesion is syphilitic The latent syphilitic patient falls heir to the same nonspecific skin and mucosal lesions as does the nonsyphilitic patient, and therefore some regard must be given to the clinical diagnosis of mucocutaneous lesions It is not within the scope of this book to go into the detailed differential diagnosis of all the skin lesions which might be simulated at times by secondary syphilis For such an analysis the reader must consult textbooks on dermatology It is my intention merely to select for brief discussion those skin diseases which are frequent enough to need to be differentiated at times from the manifestations of secondary syphilis Of assistance in diagnosis

is the fact that palmar and plantar lesions are suggestive of syphilis. Mucous patches and/or moist erosions about the genitalia, or condylomata lata, when present, constitute strong evidence in favour of secondary syphilis.

ACUTE ERUPTIVE FEVERS (measles, smallpox, etc.) may be differentiated from macular or maculopapular syphilides by the fact that they are usually ushered in by certain prodromes and present a rash of more rapid development than the roseola of secondary syphilis. Only very rarely are syphilitic skin lesions vesicular. Syphilitic manifestations persist much longer if not treated than do the rashes of the exanthems. The pharyngeal symptoms in the syphilitic do not approach those of the exanthem in discomfort or severity.

ACNE VULGARIS presents inflammation with tenderness, a 'hot' inflammatory process, and a tendency to acute exacerbations. The pustular syphilide, or moist papule of secondary syphilis, appears more indolent and is not tender.

PITYRIASIS ROSEA, a disease associated with a variable amount of itching, is distributed mainly over the trunk and upper parts of the extremities, and does not involve the palms or soles. The individual lesions, of maculopapular or papular type, are red and oval with their long axis following the segmental lines about the trunk, they are more superficial, not so infiltrative as the syphilitic papule, and are covered with a crinkly thin scale. A "mother patch" may usher in this skin disease.

SCABIES. The papules of widespread scabies may superficially suggest a papular syphilide. This infestation has a predilection for the wrists, the interdigital skin, and the abdomen, and is associated with intense pruritus. It is not unusual to encounter involvement of the skin of the trunk, buttocks, scrotum, and penis. The scratch marks usually accompanying scabies indicate that the lesion is not syphilitic. Since both diseases have their highest incidence in the lower economic classes of society, a confusing picture of both scabies and the maculopapular rash of secondary syphilis may be found in the same patient.

TINEA VERSICOLOR is a fungus infection with lesions usually of many months' duration. It appears as macular lesions which tend to become confluent and often involve large areas. The lesions are of a fawn colour, and have a branny scale. The upper part of the chest and back are the most common sites of involvement.

PSORIASIS presents skin lesions consisting of elevated plaques covered by a silvery scale which, when removed, leaves bleeding points. It has a predilection for the scalp, the sacral region, and the extensor surfaces of the extremities (elbows and knees). If palmar and plantar lesions do occur in this disease the scaling is more marked than in the case of secondary

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sypilis of the same site. Rarely, however, as we can attest, sypilis may simulate psoriasis in almost all details.

**SEBORRHEIC DERMATITIS** consists of macular lesions at the hairline, back of the ears, over the sternum, between the scapulae, in the axillae and in the inguinal regions. A greasy scale covers the areas, at times they may assume a weeping, eczematous appearance.

**LICHEN PLANUS**, characterized by severe itching, has a tendency to appear on the flexor surface of the wrists and anterior aspect of the legs, and may present lesions in the oral mucosa. The individual lesions are flat, angular, of a violaceous colour, and are covered with fine adherent scales. The penis may be the site of such lesions.

**TRICHOPHYTOSIS** (ringworm) may suggest an annular syphilitic. The fungus may be demonstrated by treating the scales with an alkali. Scaling is more common than in sypilis, and the elevated border contains punctate vesicles or pustules. There is less induration of the borders than in the annular syphilitic lesion. Itching is common.

**DRUG RASHES** may simulate many skin diseases, and therefore have no special characteristics. Only by being aware of this fact can inquiry be directed to learn of the use of drugs in unusual or atypical skin diseases.

**CONDYLOMATA ACCUMINATA** (venereal warts) tend to appear as groups of pink cauliflower-like growths up to the size of a pea, but may be grouped so thickly that the vulva, for example, may be completely covered by a mass of these lesions. They are firm, and feel cartilaginous when scraped with a scalpel in an attempt to obtain material for darkfield examination. Typically they are pedunculated, and appear on the vulva and perineum in the female. In the male they may be found under the prepuce, on it, on the glans, at the corona, or on the scrotum. Usually close examination differentiates venereal warts from the condylomata lata of sypilis, but it must be realized that examples of both types of condylomata are not uncommon on the genitalia of the same patient.

**GRANULOMA INGUINALE**, upon its first appearance as a single papule or as several scattered papules, may simulate the condyloma latum. As it spreads, differentiation is not difficult. The early painless papule may be distinguished from a syphilitic condyloma only by a negative darkfield examination or the demonstration of Donovan bodies.

**HEMORRHOIDS** may be the diagnosis upon a hasty glance at one or several condylomata lata of the anal region. Careful inspection usually rules out hemorrhoids leading to the use of laboratory methods for the diagnosis of sypilis.

**CARCINOMA** of the genitalia may present itself as a papule which, if eroded, might suggest the condyloma latum. The hardness of such a lesion

and the negative darkfield examination will rule out syphilis. Biopsy is essential in making the diagnosis of malignancy.

At times the differentiation of mucous patches from non syphilitic lesions of the oral mucosa constitutes a real problem.

**TRAUMA**, as from biting the buccal mucosa or the lip, may produce excoriation which may closely simulate a mucous patch. The history, the pain, and tenderness point to the trauma of biting or of a cigarette burn.

**HERPES SIMPLEX** Usually this disease is characterized by the appearance of a cluster of vesicles. As such, confusion with syphilitic secondary lesions is not likely to occur. After the vesicles have broken and become confluent, however, the resulting lesions may simulate mucous patches. In the mouth a herpetic lesion appears as aphthous stomatitis (canker sore), a superficial ulcer, on the buccal mucosa, on the gums, and under the tongue. These ulcers, in contrast to the typical mucous patches, have a fine red border and are very sensitive to trauma, hot food, and condiments. A history of recurrent lesions over a period of many years is characteristic in herpes.

**ACUTE FOLLICULAR TONSILLITIS** may give an appearance much like that of mucous patches on the tonsil. The symptoms of acute infection are much more pronounced than one expects to see in secondary syphilis. The fever, chilliness, and other manifestations of systemic reaction are more marked in streptococcal diseases. The sore throat and discomfort on swallowing are more pronounced, and the mucosa is more red and angry in appearance than in acute syphilis.

**VINCENT'S INFECTION** frequently is associated with a membrane on the tonsils, pillars, and soft palate, and may imitate mucous patches. A Vincent's infection may be accompanied by ulceration, and will cause more severe systemic reactions than secondary syphilis. The organisms can be demonstrated by smear.

**RIBOFLAVIN DEFICIENCY** may present the cracked lip as in syphilis, also unassociated with pain. Both diseases may present noninflammatory fissures at the angles of the mouth. Deficiency cheilosis may be accompanied by the characteristically magenta-coloured tongue.

**TUBERCULOSIS** of the mucous membrane of the pharynx, tongue, mouth, or lips is usually characterized by multiplicity of lesions. It is practically always associated with the symptoms and signs of advanced pulmonary tuberculosis. Tuberculous mucosal lesions usually are very painful as compared to the mucous patches of syphilis.

**MOIST LESIONS AND EROSIONS ABOUT GENITALIA** As is true of the manifestations of secondary syphilis in the oral and pharyngeal mucosa, so too the moist lesions or erosions about the genitalia of either sex may give rise to difficulty in differential diagnosis.

**TRAUMA** Depending upon the type of injury and the site of its application, moist erosions may be closely simulated by traumatic lesions. Forced or violent intercourse, especially with a tight introitus, may cause superficial erosions at the posterior fourchette and about the introitus generally. The rubbing of vulval pads, especially with uncleanness, may produce excoriations on the vulva. In the male with high grade phimosis, upon erection and intercourse, a rosette of a dozen or more small fissures or cracks may appear radially at the edge of the foreskin ('haircuts'). The application of chemicals such as iodine for benign lesions of the glans penis may produce "burns" at the corona. In the female, douches of liquor cresolis saponatus and other substances in too concentrated a solution may cause superficial chemical burns with denudation or erosion of the membranes. All of these nonspecific lesions at times cannot be differentiated from the moist erosions of secondary syphilis without darkfield examination.

**PELLAGRA** Characteristically vitamin B complex deficiency presents glossitis and dermatitis, especially of the exposed skin surfaces, as at the neck and the dorsum of the hands and feet. Less commonly, the skin of the genitalia is involved by the pellagrinous dermatitis, and denuded areas with serous secretion may be found on the penis, the inner surface of the prepuce, on the glans, scrotum, and perineum. Within the year, a patient with such skin lesions and a glossitis was referred to the Syphilis Clinic with the diagnosis of secondary syphilis. The mucosal changes in the mouth and the moist genital lesions were thought by the referring physician to represent acute syphilis.

**CHANCROID** The soft chancre and its differentiation from the primary lesion of syphilis was discussed under that heading. (See Chapter vi.) Since this nonindurated lesion may be a superficial ulcer it may be confused, at times, with the erosions of secondary syphilis on the genitalia.

**LYMPHOPATHIA VENEREUM** The evanescent primary lesion of this genito-infectious disease may appear as either a superficial moist erosion of the genitalia or as a small papule which becomes eroded. Differentiation from secondary syphilitic lesions is possible only by the use of the darkfield examination and the blood tests for syphilis. The subsequent development of buboes and a positive Frei test in lymphopathia venereum establishes the diagnosis. Many patients developing this disease also have syphilis, either clinical or latent, and therefore a positive blood test for syphilis does not necessarily mean that the genital lesion is due to *T. pallidum*.

**EROSIVE BALANITIS** Uncleanness, phimosis, and retention of smegma may predispose to secondary infection. Because of this the mucosa may become denuded in areas on the inner aspect of the prepuce and on the glans. Such erosions may simulate lesions of secondary syphilis.

**HERPES GENITALIS** Herpetic lesions are not unusual in either sex. A history of their recurrence for years is common and helpful in diagnosis. Recurrence of herpes with the menses is not infrequent. Characteristically, if observation by the patient has been accurate, a cluster of several vesicles appears attended by a burning sensation and itching. After a few days the vesicles rupture and leave superficial, moist erosions which may be indistinguishable from the moist lesions of syphilis. Fortunately the history may be so excellent as to leave little doubt relative to the diagnosis.

**APHTHOUS ULCER** This painful superficial ulcer is most likely to occur on the labia or at the introitus. The ulcer is shallow, often with a yellowish exudate on the base. Aside from its appearance, differentiation from syphilis must depend on the use of the darkfield examination and serologic tests.

**ANAL FISSURE** Such an innocent lesion would not often be suspected of being syphilitic in the absence of other manifestations of secondary syphilis. Yet, in the presence of a generalized lymphadenopathy suggestive of recent syphilis, we have been able to settle the immediate diagnosis by demonstrating the *T pallidum* by darkfield examination of material obtained from such fissures.

In the differential diagnosis of the mucocutaneous lesions of the secondary stage of syphilis, the darkfield examination is essential. The presence of the *T pallidum* proves the lesion in question to be that of early syphilis. A negative serologic test which is acceptable rules out secondary syphilis. *A positive blood test for syphilis does not prove that the lesion in question is syphilitic.* The majority of the nonsyphilitic lesions which have been described for differential diagnosis will be seen at some time or another in any of the stages of syphilis.

#### OTHER CLINICAL MANIFESTATIONS OF THE SECONDARY STAGE OF SYPHILIS

The foregoing discussion has covered the lesions of secondary syphilis of especial interest to the epidemiologist, because of their relationship to the transmission of syphilis. They also are the ones which are interesting to the dermatosyphilologist. There is, however, another group of manifestations which necessarily is of concern to the general practitioner because of the clinical implications. A brief description of these clinical pictures is essential because too frequently the physician thinks of secondary syphilis only as a disease of the mucocutaneous structures. The following clinical entities can, of course, occur with or without the mucocutaneous signs. The differential diagnosis of these syphilitic manifestations will be briefly indicated in each case.

**Pharyngitis** A diffuse pharyngitis, unaccompanied by mucous patches,

is a frequent finding in early syphilis. In fact, it may be the original and only complaint bringing the patient to the physician. The appearance of acute syphilitic pharyngitis is difficult to describe with certainty, yet there are certain features that arouse suspicion of syphilis. Inspection of the throat suggests edema of the soft palate, uvula, and tonsillar pillars. The colour is more violet than red or pink. Pain is not prominent, rather there is discomfort on swallowing. Although the constitutional symptoms of fever, malaise, and general aching suggest an acute upper respiratory infection, the story of chronicity (in weeks), the absence of pain, and the lack of the redness of bacterial infection should raise the question of acute syphilis (Case 46).

**Laryngitis** Hoarseness may accompany the secondary stage of syphilis. Examination with the laryngeal mirror may reveal an edematous infiltration of the laryngeal structures and mucous patches may be present.

**Lymphadenitis** A generalized enlargement of the lymph nodes is a characteristic finding in the majority of syphilitic patients in the secondary stage. The glands harbour many treponemata as may be shown by the case with which lymph gland material may be used to transmit syphilis from rabbit to rabbit in experimental work.

The glands in the cervical, axillary, and inguinal regions may reach the size of a hickory nut, and at times are even larger. Often as the neck is rotated the posterior chain of cervical nodes stands out prominently and can be recognized at a glance. The epitrochlear nodes at times may be so large as to be visible. As part of the general lymphoid hyperplasia the spleen is not uncommonly palpable in the secondary stage.

THE DIFFERENTIAL DIAGNOSIS in the presence of a generalized lymphadenopathy includes lymphatic leukemia, Hodgkin's disease, lymphosarcoma, tularemia, and infectious mononucleosis. The latter is of especial importance, for it is a disease of young people and not infrequently is accompanied by a positive precipitation test, as was brought out in Chapter IV. A blood smear will assist in the differentiation of leukemia and infectious mononucleosis from secondary syphilis in cases showing only constitutional symptoms and lymphadenitis. The heterophile antibody reaction is also of value.

**Arthritis** As was noted in the earlier paragraphs of this chapter generalized aching referred to joints and muscles is very common as one of the systemic manifestations of syphilis in the secondary stage. More definite localization of such symptoms to specific joints does occur, however, and may be the only obvious manifestation of acute syphilis. In several patients I have made the error of diagnosing a common arthritis of one type or another, to find subsequently that acute syphilis was the etiologic factor.

Subjectively, the patient complains of pain referred to one or more joints, and limited motion leading at times to definite disability. Examination may reveal some swelling of the joint, and occasionally fluid may be demonstrated in a large joint such as the knee. Pain on movement may be present, tenderness is demonstrable, but there is not the heat or redness of an acute bacterial process (Case 41)

**Case 41** A twenty-one-year-old, unmarried Negress had been under observation in the Gynecology Clinic for a period of two years because of lower abdominal pain and trichomonas vaginitis. Blood Wassermann and Kahn tests had been negative upon several occasions during that period of time. She then complained of painful and stiff joints. At about this time her blood was found to be positive in both the Wassermann and the Kahn tests, and she was referred to the Syphilis Clinic. Here it was found that the arthritic manifestations had been present for two months. Numerous joints had been involved. The pain was especially worse at night. She gave no history suggestive of acute syphilis, but she had been sexually promiscuous until the onset of the arthritis.

Examination revealed pain and stiffness of the right shoulder and both hips upon passive motion. There was some tenderness over these joints, and slight crepitus was noted in the right shoulder joint. There was no local heat at any joint. The tonsils were enlarged and red. There was prominent generalized lymphadenopathy. No skin lesions were present. Material from an erosion of the uterine cervix was darkfield negative. The blood Wassermann and Kahn tests were positive upon two occasions. The blood smear did not reveal the picture of infectious mononucleosis.

**Comment** This patient presented the picture of arthritis which is not uncommon in secondary syphilis. Generalized lymphadenopathy was compatible with the diagnosis. The proof of the diagnosis lay in the therapeutic result. Although the patient had had constant discomfort and partial disability for two months, all symptoms disappeared on the fourth day after the second injection of an arsenical, or eleven days after the first injection. There was a remarkable reduction in size of the lymph nodes after the fifth injection of arsenic.

IN THE DIFFERENTIAL DIAGNOSIS, early rheumatoid arthritis is the most likely condition to be simulated by acute syphilis. My errors in diagnosis have involved this condition, or acute infectious arthritis, although the redness and heat are lacking. (Incidentally, a generalized glandular enlargement may accompany rheumatoid arthritis.) A complete physical examination for other evidences of acute syphilis, the use of serologic tests and therapeutic results of antisyphilitic treatment, will eventually settle the problem. Some authors have described a highly acute process simulating rheumatic fever. Such a case has never fallen within my experience.

**Periostitis and Osteitis** Unquestionably some of the pains referred to the extremities in acute syphilis have their origin in involvement of the periosteum. The changes are usually too slight to be shown by the

roentgenogram Tumefaction over the site of periosteal or osteal syphilis may occur, this, as well as pain, may lead to the clinical diagnosis of bone syphilis In the Vanderbilt University Hospital Syphilis Clinic the diagnosis of bone involvement in the secondary stage of syphilis has been verified in only five cases by roentgenologic examination, however In these instances the roentgenologic and clinical pictures were identical with that of tertiary syphilis of bone Hence, the reader is referred to the discussion on bone syphilis in Chapter v

**Ocular Syphilis.** The eye may be involved occasionally in secondary syphilis The manifestations are chiefly iritis and neuroretinitis Ocular involvement occurred in only about 2 per cent of 1,237 cases of secondary syphilis

**IRITIS OR IRIDOCYCLITIS** is the more common ocular lesion While it may occur very early in the course of the secondary stage, it is seen more often some months later The symptoms of syphilitic iritis are no different from those of iritis due to other causes although I believe they are often milder Photophobia, pain referred to the eyes, lacrimation, and impaired vision are typical complaints The process appears usually first in one eye, to be followed some days later by involvement of the second Examination reveals the violaceous circumcorneal injection, often there is an accompanying conjunctivitis and edema of the iris If the condition has been of some duration, the pupil may be irregular, and may react with a limited range because of the inflammation of the iris with its adherence to the anterior lens capsule (An irregular fixed pupil often results from adhesions to the lens capsule Such a pupil reacts neither to light nor accommodation, and must be differentiated from the Argyll-Robertson pupil of neurosyphilis) The borders of the cornea may show some steaminess due to the inflammatory process, and represent a kerato iritis (Case 42)

**Case 42.** A thirty-four year-old white widow was referred to the Syphilis Clinic from the Otolaryngology Clinic About four months before she developed pain in the eyeballs, lacrimation, photophobia, and redness of the eyes Within the month before admission she had had a tonsillectomy and three dental extractions—presumed foci of infection She was then referred to the Vanderbilt University Hospital Otolaryngology Clinic because of "cloudy sinuses" found upon roentgenologic examination In this clinic examination of the sinuses was negative, but a maculopapular eruption was noted upon her arms The patient was accordingly referred to the Syphilis Clinic, where she admitted frequent sexual exposures since her husband's death ten years before She had been aware of a rash for several months, but denied a primary lesion

Examination revealed a maculopapular rash of the upper and lower extremities and shoulders in addition to the findings of iritis The blood Wassermann and Kahn tests were positive

**Comment** In this case syphilis as the cause of iritis had been overlooked by attending physicians, and possible foci of infection had been removed. It was only when the keen eyes of the consulting otolaryngologist noted the eruption upon the arms that the diagnosis of syphilis was made. Both iritis and rash cleared completely with three injections of an arsenical.

**NEUORETINITIS** is seen less frequently than iritis. The patient may complain of visual impairment. Fundus examination may reveal edema of the nerve head, and patches of exudate in the retina (Case 98).

The diagnosis of the syphilitic nature of iritis or neuroretinitis is not possible on examination. Only other evidences of acute syphilis may lead to the proper diagnosis. Identical pictures of iritis or neuroretinitis may occur in gonorrhea, tuberculosis, rheumatic fever, influenza, and focal infection, and cannot be differentiated one from another by inspection alone. Only the physician who is trained to think of syphilis in connection with these eye conditions will use serodiagnostic tests to aid in the diagnosis.

**Hepatitis** Rarely jaundice may be part of the picture of secondary syphilis, occurring at the time of the secondary rash or appearing some weeks later. The pathology accounting for the jaundice is not definitely known, but it is presumed to be a 'roseola of the biliary passages'. This implies a diffuse inflammatory reaction involving the biliary canaliculi. Jaundice may become quite intense, and may be associated with acholic stools. In untreated syphilis icterus may persist for weeks. Examination usually reveals, in addition to icterus, a palpable tender liver.

Differentiation from catarrhal jaundice offers the most common diagnostic problem, especially since some degree of fever is common in secondary syphilis. A skin rash, generalized lymphadenopathy, a positive blood test for syphilis, and the results of antisymphilitic treatment will make the diagnosis of acute syphilitic hepatitis. (See Case 47, hepatorecurrence.) The gastro intestinal symptoms which usually usher in catarrhal jaundice are lacking. With extreme rarity syphilitic hepatitis of the secondary stage progresses to acute yellow atrophy. A few such cases have been reported. Jaundice appearing after the use of arsenotherapy in acute syphilis raises the diagnostic problem of the Herxheimer reaction as against arsenamine hepatitis.

**Nephrosis** A nephrotic syndrome may appear in the late primary or early secondary stage of syphilis. No report of an uncomplicated picture of the pathology in this condition has ever been published. A recent report from our clinic added three to the few acceptable cases which have been described in the literature. In this report the clinical characteristics of this nephrosis are summarized as follows: with an abrupt onset, the typical features include massive edema, albuminuria, low total blood-serum



proteins with partial depletion of the albumin fraction, oliguria, elevated blood cholesterol, strongly positive serologic tests for syphilis, and finally, prompt recovery following antisyphilitic treatment. The picture may be fleeting, and clear quite promptly without treatment. The sudden onset of a nephrotic picture in a patient with acute syphilis should bring this condition to mind.

**Cardiovascular Syphilis** Without question, invasion of the aortic wall occurs in the early stages of syphilis. Since for practical purposes cardiovascular syphilis is generally a manifestation of the second decade of the disease, no details will be considered at this point. Rarely, however, the invasion of the aorta may lead to advanced aortic disease in a relatively short time following infection.

**Central nervous system Syphilis** It was indicated in Chapter 11 that with general invasion of the body by *T. pallidum* the central nervous system also is involved. In the secondary stage of syphilis, central nervous system invasion may be entirely asymptomatic, manifested only by spinal fluid changes. Acute syphilitic meningitis may be the presenting condition in this stage of syphilis, however. Since the progress of neurosyphilis may extend over many years to its ultimate late manifestations, I prefer to discuss the entire subject of neurosyphilis in a separate chapter.

## PROPHYLAXIS

Education of the public relative to the genito infectious diseases in addition to whatever moral deterrents operate in a given individual is of prime importance in the universal hope that these diseases may in time be reduced to the absolute minimum. The more widespread that effective sex instruction and education with respect to venereal disease become, the more one may hope that sexual promiscuity will be reduced. It is a fact, however, that man is an animal with certain biologic instincts which in some individuals, cannot be controlled by knowledge of the risks attendant to sex contact. Therefore the physician, at least, must discard the attitude of assuming that venereal disease is a visitation for sin, and face the fact that syphilis and the other genito infectious diseases are transmitted by certain pathogenic organisms, and that these infections can, in some measure at least, be prevented.

### CHEMICAL PROPHYLAXIS

In the armed forces of this country chemical prophylaxis is urged on all men following every sexual exposure. After experiences with this phase of syphilis control with the A.E.F. in France during the First World War, Ashburn, Moore, Walker, and others emphasized the efficacy of prompt institution of chemical prophylaxis. Although in the civilian population

there is little demand for this type of prophylaxis, I shall quote the routine as recommended in Supplement No 6 to the Venereal Disease Information published by the United States Public Health Service in 1938

**Technic of Prophylaxis for the Male** If possible do not allow the patient to administer the treatment to himself. The patient is made to urinate. He is provided with a basin of warm water and a gauze wipe, with which he washes the genitals thoroughly while liquid green soap is dropped on the penis. The washing to be done thoroughly should consume about ten minutes, and should include the penis, scrotum, pubis, and the adjacent areas of the thighs. Use especial care to wash thoroughly the folds of the frenum and foreskin. After washing, the parts should be dried thoroughly. The washing with soap and water is important, soap is the only part of the treatment effective against chancroid, and is also of value as a destroyer of the organism of syphilis. Before proceeding further the presence of urethral discharge or genital sores is noted.

The next step is the injection of 1 dram (4 cc) of a freshly made 2 per cent protargol solution (or a 10 per cent solution of argyrol) into the urethra by the physician. The patient then holds the meatus firmly between the thumb and forefinger for five minutes, from time to time allowing a drop to escape from the meatus so that all parts of the urethra are in contact with the solution. At the end of five minutes the protargol is allowed to escape, without pressure or stripping, so that a few drops remain. One half to 1 dram (2 to 4 Gm) of 33 per cent calomel ointment is next rubbed thoroughly by the patient, under the observation of the physician, into all parts of the penis for five minutes, special attention being paid to the retracted prepuce, the frenum, and the glans. The scrotum also should be rubbed with ointment. The genitalia are then wrapped in toilet paper or waxed paper to protect the clothes, and the patient is instructed not to urinate for four or five hours.

**Technic of Prophylaxis for the Female** In cases of rape, and in some others, there may be occasion for applying early treatment to females. If such occasion should arise, the following procedure is suggested. Have the patient urinate. Place the patient in the lithotomy position. Wash the genitals and adjacent parts with soap and water. Give a douche of two quarts of sterile water, temperature 100° F, followed by two quarts of 1:2000 mercuric chloride solution, and wash external parts with the latter. Dry the vagina and vulva by sponging. Swab the entire vagina, through a speculum, with a 2 per cent protargol solution, or 10 per cent argyrol solution, freshly made, reach every fold and especially the posterior vault and external os. Swab the entire vulva in the same way, reaching every recess. Inject enough of the same solution into the urethra to distend it moderately and let the patient hold her finger (in a rubber glove) against the meatus to retain the solution for from three to five minutes.

Douche the vagina and vulva with a small amount of sterile water, and sponge dry with gauze. Apply calomel ointment to the cervix, vagina, vulva, and adjacent parts, rubbing thoroughly into the recesses and folds of the mucous membranes and skin, and taking at least ten minutes for the operation. Do not use more than 4 Gm (1 dram) of calomel ointment in the vagina. Cover the

external parts securely with oiled silk or waxed paper, and instruct the patient to allow ointment to remain for several hours before washing the parts

Chemical packets for prophylaxis are on the market, but it is my impression that they are little used. Because of education received in the armed forces I have found that some ex service men use this form of prophylaxis. Obviously chemical prophylaxis as used in the Army and Navy will but rarely be followed in civilian practice. The lack of instruction of the necessity of prophylaxis, the lack of the threat of penalties and the absence of military police in 'red light districts' to enforce prophylaxis all conspire to make chemical prophylaxis unworkable in everyday practice.

#### MECHANICAL PROPHYLAXIS

Mechanical prophylaxis by the use of the condom is the most practical method of diminishing the rate of venereal disease. It has the further advantage of protecting both parties in illicit sex contact, which is probably more to the point in such cases than in the case of sexual relations with the professional prostitute. Of course the users must not be deluded by such beliefs as have been described in the chapter on history taking. The user must be instructed as to the need of using the condom before as well as during actual intercourse. Even with proper use the sheath does not offer complete protection. We have encountered chancres at the base of the penis where protection is impossible (Case 11). The greatest difficulty which presents itself is the education of the public to the use of the condom. In certain classes this is impossible. It is inconceivable, for example, that among plantation Negroes, where the incidence of syphilis in the sexually active age groups is as high as 40 per cent, mechanical prophylaxis would be used. Such a Negro would be unable to purchase the condom in the first place, and would refuse to use it in the second.

#### ARSENICAL PROPHYLAXIS

Arsenical prophylaxis is a much debated subject and in general, syphilologists are strongly either for or against its use. The question arises most often in cases of innocent exposure to infection as in professional personnel, physicians, nurses and dentists. The question rarely arises in lay practice. Occasionally a person presents himself having had sexual exposure with a person found later to have syphilis.

Exposure in professional work might be avoided by obtaining serologic tests for syphilis before instead of after operation. A positive preoperative blood test, followed by some therapy, except in emergency operations, would reduce the number of instances of need for worry because of puncture wounds at operations. The use of arsphenamine prophylaxis

implies that the doctor or nurse has acquired syphilis by a needle or scalpel puncture wound. If arsenic is used the person should receive at least a whole course of arsenical (eight to ten) injections and then be followed for life as in the case of any syphilitic patient. Treatment should be given no later than forty-eight hours after exposure (Moore). That two injections of arsenic may merely delay and not control infection is probable. (We have seen a patient who had one extramarital sex exposure. The next day, after a friend had told him his contact had syphilis, he received a full dose of neoarsphenamine which was repeated three days later. His blood tests were negative at this time. Serologic tests for syphilis were done at intervals. They remained negative for some four months, and then were found to be positive upon repeated examinations. His wife's blood test at this time was negative.) Not infrequently physicians and nurses acquire puncture wounds at darkfield work or venipuncture in patients with acute syphilis. Yet syphilis rarely develops. Therefore it seems best to open the puncture site and rub mercury ointment into it for twenty or thirty minutes, and then await the appearance of a primary lesion. Frequent blood tests must be done in the following three months because infection may be of the d'emblee type.

### TREATMENT OF ACUTE SYPHILIS

The treatment of syphilis in the acute phase, either in the primary or secondary stages, has been standardized as the result of studies made by the Co-operative Clinical Group. Since this standardized treatment has been commonly accepted and urged upon the practitioner by state and national health agencies, I shall present this form of treatment without discussion as to the background of the experiences in the various clinics which led to the adoption of the continuous plan of treatment. The reader who is interested in this and the efficacy of other plans of treatment is referred to the various papers by the Co-operative Clinical Group. It must not be thought that this plan of treatment is universally accepted. In fact, variations of this scheme are used in the clinics of the men making up the Co-operative Clinical Group. The treatment plan advanced by them is probably a compromise. I feel that this commonly accepted plan should be presented here since it is so widely used. The objectives of treatment in early syphilis are two. One is to obtain "cure"—the complete obliteration of the syphilitic infection. The second is to control the infectiousness of the patient. Therefore, the therapeutic agents especially effective in early syphilis are used in adequate dosage and in sufficient numbers of injections in an attempt to attain these ends. *In the treatment of early syphilis there is no place for inadequate dosage or short courses of the arsenicals nor place for rest periods from treatment, as may be the case in*

late syphilis Treatment must be continuous, consisting of alternating courses of arsenic and bismuth (Mercury has been shown by the Co-operative Clinical Group studies to be markedly inferior to bismuth in the treatment of early syphilis )

Though a definite schedule is set up for the treatment of early syphilis, more prolonged therapy may be indicated It is generally accepted that the accompanying plan is ideal if serologic reversal occurs within the first ninety days and if the spinal fluid is found to be negative The Co-operative Clinical Group recommends continuous treatment in early syphilis until the blood tests have been negative for at least one year If serologic reversal does not take place, treatment should continue for at least two years It is our plan in such cases to give two courses of twelve weeks of bismuth with intervening three month rest periods in the third year This is not necessary very often

Serologic tests for syphilis should be carried out at intervals as a gauge as to the efficacy of treatment and with respect to the possibility of complications such as asymptomatic neurosyphilis In the Vanderbilt University Hospital Syphilis Clinic blood samples are obtained every second to fourth week in early cases until serologic reversal takes place Thereafter, tests are done at the end of each course of treatment with arsenic or bismuth This is rather impractical in the public health clinic or in practice It seems to be sufficient in practice to take blood samples as follows after three, six, and twelve months of treatment, and at the end of treatment. If treatment has been irregular or complications have occurred, this schedule does not apply

In the treatment schedule set up by the Co-operative Clinical Group it is advised that spinal fluid examination be carried out at the end of the first course of arsenic As an ideal procedure this is endorsed, but it is equally well recognized that this will not be done by the practitioner Spinal fluid examinations must therefore be kept to a minimum My feeling is that if lumbar puncture can be done toward the end of the course of treatment, at about ten to twelve months, let us say, a practical end has been accomplished If blood and spinal fluid are both negative, well and good, and if the patient should cease treatment as the result of lumbar puncture, the major amount of treatment has been given Because of the likelihood of asymptomatic neurosyphilis, I would urge spinal fluid examination at the end of six months if serologic reversal in the blood had not been obtained with good and regular treatment This attitude regarding spinal fluid examination may not be good practice in the well organized syphilis clinic, but I believe it constitutes good medicine in the usual individual practice

Subsequent to the completion of treatment, it is our custom to request

the patient to return after a period of three months' probation. At this time he or she is examined for evidence of mucocutaneous relapse, and a blood test is made. If all is negative a second three months of probation is allowed, at the end of which time the same procedure is carried out, and if again all is negative, a six-months' probation period is permitted. If at the end of this time the physical and serologic review is negative, the patient is advised to have an examination and blood test annually. (About 50-60 per cent of our patients co-operate in this.) After some years have elapsed since the termination of treatment, the examinations are made with less attention to possible mucocutaneous relapse and with more attention to possible late manifestations. This statement is made for the benefit of health officers who often have large numbers of patients to care for in a given clinic period.

Spinal-fluid examination, when negative, is never repeated if the patient is under regular observation as indicated in our plan of follow-up, except in the event of serologic relapse in the blood. In this case spinal-fluid examination is carried out immediately because of the possibility of neurorelapse.

The Co-operative Clinical Group scheme of treatment is based on the use of old arsphenamine. Such a schedule calls for thirty-two injections of arsphenamine, and forty of bismuth. Old arsphenamine has been the drug of choice in the treatment of early syphilis in the Vanderbilt University Hospital Syphilis Clinic. However, since this book is for use by the general practitioner or health officer, consideration of the use of old arsphenamine is beside the point. In spite of its recognized advantages, its use in ordinary practice is impracticable. Cole modified the treatment schedule of the Co-operative Clinical Group in 1936 for the use of neoarsphenamine, and provided for forty injections of neoarsphenamine and forty-four of bismuth. This plan of treatment is applicable by the physician in general practice. I have modified this slightly in the treatment schedule suggested in Table IX. (Full dosage of arsenic is imperative.)

A few alterations have been made in Cole's plan. It has seemed to me that the first bismuth course should be four weeks instead of six, since the tendency to mucocutaneous relapse or serologic relapse is enhanced by withholding arsenic early in the treatment of acute syphilis. Furthermore, it seems that a depot of bismuth should be established early in treatment for its treponemistatic effect, and therefore I have included one dose of bismuth with each of the first three injections of neoarsphenamine. The indicated dosage and necessary variations in the dosage of arsenicals are discussed in Chapter V. Resistance of acute lesions to arsenical treatment will be discussed in the following chapter on relapse and progression of acute syphilis.

TABLE IX  
SCHEDULE FOR TREATMENT OF ACUTE SYPHILIS<sup>1</sup>

<i>Time</i>	<i>Drug</i>
1st day { Neoarsphenamine } 5th day { and } one dose each 10th day { bismuth }	
For 7 weeks	Neoarsphenamine weekly
For 1 week	Neoarsphenamine and bismuth, one dose of each
For 3 weeks	Bismuth weekly
For 10 weeks	Neoarsphenamine weekly
For 8 weeks	Bismuth weekly
For 8 weeks	Neoarsphenamine weekly
For 10 weeks	Bismuth weekly
For 8 weeks	Neoarsphenamine weekly
For 12 weeks	Bismuth weekly
68 weeks	Totals—Neoarsphenamine—37 Bismuth—37

<sup>1</sup> Dosage of neoarsphenamine 0.45-0.6 Gm. or more dependent upon weight (See Chapter V) Arsenoxide (mapharsen) 0.04-0.06 Gm. or more may be substituted for neoarsphenamine

In an occasional case of acute syphilis, some severe treatment reaction, such as exfoliative dermatitis, may occur in the first course of arsenic. Such a complication raises a serious handicap in the adequate treatment of the patient. The only choice left is the prolonged use of heavy metal. This means a period of at least two years of injections of heavy metal with alternating periods of rest and heavy metal in the third year.

Though the above outline of treatment has become firmly established through years of study and use, I realize that we are probably on the threshold of radical changes in the management of early syphilis. Since the introduction of arsenoxide (mapharsen) has permitted both larger doses and injections at shorter intervals without untoward reactions, the trend in *experimental schemes of treatment* has been to reduce the total time needed for the treatment of early syphilis. Everyone has recognized that the major shortcoming of the above established treatment scheme is the great length of time needed for its completion. Prolonged treatment leads to loss of interest by the patient with resulting inadequacy of treatment and its unfortunate end results. Any plan which reduces the total time necessary for adequate treatment will increase the number of patients completing treatment.

The "massive-dose" or "five-day treatment" of acute syphilis has been briefly mentioned in Chapter V. Though it seems that this plan is

successful in a high proportion of cases of syphilis, the necessary hospitalization and nursing service may make this scheme impracticable.

At the time of this writing a study is being made in a number of collaborating clinics of the use of multiple doses of arsenoxide per week for periods of two to three months.

A trial of a combination of prolonged fever therapy and massive dosage of arsenic also is being made by some investigators.

The practitioner must realize that "massive-dosage" treatment, multiple injection schemes, and combined fever and "massive dosage" are purely *experimental*. Some years must elapse before the results of such trials can be evaluated, and therefore these methods should not be undertaken by the average physician.

It is of interest that the Army has adopted a modified form of abbreviated treatment as outlined in Circular Letter No. 74 of the Office of the Surgeon General (July, 1942). It is as follows:

*Week*

1		
2		
3	Arsenoxide (mapharsen)	Bismuth subsalicylate,
4	intravenously twice weekly,	intramuscularly once
5	total 20 injections	weekly, 5 doses
6		
7		
8		Omit bismuth,
9		5 weeks
10		
11		
12	Omit arsenoxide, 6 weeks	
13	Bismuth subsalicylate,	
14	intramuscularly once weekly,	
15	6 doses	
16		
17		
18		
19	Arsenoxide as in the first	Omit bismuth,
20	course, twice weekly, total	5 weeks
21	20 injections	
22		
23		
24		Bismuth subsalicylate,
25		intramuscularly once
26		weekly, 5 doses



The dosage recommended in the Army scheme is 0.05-0.07 Gm of arsenoxide, based upon the patient's body weight, and 0.2 Gm of bismuth subsalicylate. Thus the treatment adopted by the Army provides for forty injections of arsenoxide (mapharsen), and sixteen doses of bismuth in oil in a period of six months.

This modified short treatment scheme, which was developed by the National Research Council, is being given consideration by the Navy. However, its official adoption is pending.

#### PROGNOSIS AND RESULTS OF TREATMENT IN ACUTE SYPHILIS

The ultimate prognosis in the untreated syphilitic will be considered in Chapter IX. Here, the question arises as to the prognosis of acute syphilis when treated by modern methods. Inadequacy of treatment leads to the possibility of relapse, to be considered in Chapter VII.

The prognosis in early syphilis, if treatment is adequate by present-day criteria, has been studied by the Co-operative Clinical Group and by Padgett. Without taking into consideration the amount and type of treatment, the Co-operative Clinical Group found (in cases followed for two years or longer) that a satisfactory clinical outcome was more frequent if treatment was started in the seronegative stage. In 140 seronegative primary cases satisfactory outcome was obtained in 71.4 per cent, in 274 seropositive cases only in 53.3 per cent. Satisfactory outcome in 912 early secondary cases was 49.8 per cent.

According to the Co-operative Clinical Group data with the continuous plan of treatment, reversal of blood tests in acute syphilis may be expected as follows: 52.6 per cent in 3 months or less, 29.2 per cent in 4 to 12 months, 3.4 per cent in 13 to 30 months, 86.7 total reversals. "Wassermann fastness" occurred in 11.2 per cent of 1,423 early cases treated with the continuous plan.

More recently Padgett published a better evaluation of treatment results in patients followed for at least five years after the cessation of treatment which was *not* ideal. The criteria for "cure" in this study were listed as reinfection, freedom from symptoms and signs of syphilis on careful examination, repeated by negative serologic tests for syphilis, normal roentgenograms of the heart and aorta, and a negative spinal fluid. Among the 551 cases studied, 65.7 per cent were classed as "cured," 14.9 per cent gave positive blood tests for syphilis, 12.3 per cent had some form of neurosyphilis, and 7.1 per cent presented some other late lesion of the disease. Of 22 seronegative primary cases treated and followed, 82 per cent were "cured." The 69 seropositive primary cases showed the poorest results, with only 55 per cent of "cures." Of 397 cases of secondary syphilis, 68.8 per cent achieved "cure." Padgett explains this apparent discrepancy

of better results in cases of longer duration, i e , secondary syphilis, on the commonly accepted idea that treatment interrupts the development of immunity in early syphilis. In the seronegative primary stage, host immunity has not as yet developed. In the seropositive phase, a developing immunity is interrupted and thus treatment results are poorer than in the secondary stage where presumably the immunity has reached fairly high levels.

In his analysis of 551 early cases followed for five years or longer, Padgett has analysed the "cures" on the basis of the type of treatment (irrespective of amount) used in the first six months. He found that if the first six months of treatment was continuous, "cure" was obtained in 83.4 per cent of patients treated, if this plan was continued, "cure" occurred in 90.4 per cent. Irregular treatment following an introductory six months of regular treatment reduced "cure" to 75 per cent. If treatment was intermittent or irregular in the first six months, "cure" was attained in 53.2 per cent, and this result was not improved by further treatment of this type. Continuous treatment following a first six months of irregular treatment raised the "cures" to 72.7 per cent however. With respect to the number of injections of arsenic given under the continuous-treatment plan, Padgett found that "cure" occurred in only 35.3 per cent of 17 patients who had no treatment at any time, in 66 per cent of those who had 10-12 injections of arsenic, and in 81.7 per cent of those who received more than 20 injections of an arsenic.

Some comments made by Moore in a discussion of Padgett's paper are worthy of inclusion here. He points out that this is the first long-term study of the results of treatment in early syphilis. Of practical interest for the general practitioner and clinic physician is his conclusion, that vigilance relative to late manifestations can be relaxed in early cases after a five-year period of "cure." In the early cases at their clinic, if examination and serologic tests for syphilis were negative at five years, they were the same five or more years later. Lastly, Moore points out that by the use of the standard present-day methods of treatment 90-95 per cent of patients placed under treatment in the early stage can expect a "cure."

### ADVICE TO THE PATIENT

Following the unquestioned establishment of the diagnosis of acute syphilis, either primary or secondary, by *clinical manifestations and either a positive darkfield examination or a definitely positive serologic blood test for syphilis* certain matters should be taken up with the patient.

The patient should be informed of the diagnosis, and in doing so one must, depending upon the patient's educational level, use such terms as can be understood—as "syphilis," "the pox," "syph," and "bad blood." I

believe it is unjustifiable at the present time to treat a patient while he is kept in ignorance of his or her condition. The family approach in the epidemiologic work as used in our clinic (Chapter xvii) has avoided all but a few marital misunderstandings. Fewer difficulties arise as the result of a frank discussion of the diagnosis than by the doubts which would arise with the increasing general knowledge of the reason for "shot treatment."

Having acquainted the patient with his diagnosis and what it means with respect to infectiousness, disease in later years, and effects in the offspring, the plan of treatment should be outlined. I believe that knowledge of the diagnosis and its meanings provides a more co-operative patient, anxious to be regular in his treatment and to complete the course. This is also the time at which the patient must be forewarned that a negative blood test during treatment does not mean that "cure" has been attained. Thus one can counter advice by the patient's lay friends regarding the need for further treatment. So too the patient can be prepared for possible "Wassermann fastness" and avoid subsequent syphilophobia if and when treatment is deemed to be sufficient in spite of a positive blood test.

The patient must be instructed as to his infectiousness, and an attempt must be made to arouse in him a sense of responsibility both to avoid transmission of the infection to others, and also to assist in the investigation of his contacts. (See Chapters xvii and xix.) He should be made to see that in the presence of open lesions he must use care in the matter of dishes, towels, and anything that may be used as a vector, including douche and rectal tips and the like. The interdiction of kissing and sexual contact is of course obvious. What is practical in this respect is difficult to decide. I know that in the case of promiscuous persons—as in many Negroes, for example—one cannot hope to enforce any considerable period of sexual abstinence. Too often have I asked the promiscuous young Negress with condylomata, who is under treatment and has been advised regarding infectiousness, as to her sexual activity and obtained the admission of sex exposure. Certainly, from the results of our darkfield examinations I feel that as long as treatment is regular much syphilis is being controlled even in the face of resolving condylomata. Even in the married state there is a limit to which sexual abstinence can be carried out and the home still be maintained. It seems probable that about the most one can do with the human being, constituted as he is, is to interdict kissing and sexual contact until the second course of arsenic has been well entered. I am always dubious about the first bismuth course, since infectious relapse may occur at such time. Even when sexual intercourse is again taken up, the use of a condom for sex play as well as actual intercourse is essential. Only the co-operative patient will do this and continue its use for a year after treatment ceases.

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syphilis, having seen untoward effects of treatment with arsenic, develop a fear of the drug. Their conservatism leads them to use small doses with the hope of avoiding possible trouble. We have seen, repeatedly, acute syphilis in adults treated with doses of neoarsphenamine as small as 0.15-0.3 Gm. Such dosage does little to impede the course of the infection, and in fact does the patient more harm than good, for it neither eradicates the infection nor permits the host to develop his natural resistance to the infection. It must be emphasized that adequacy of dosage in acute syphilis varies with the size of a patient, for obviously a man weighing two hundred pounds requires more arsenic than a man weighing one hundred and fifty pounds. In Case 44 relapse occurred and lesions persisted because of inadequate dosage.

**Case 44.** A thirty year-old white housewife was admitted to a hospital with the diagnosis of typhoid fever 7.5 months previously. During her convalescence she was told she needed "shots." She received sixteen injections of neoarsphenamine, and one of bismuth. After the first injection a circular lesion appeared on the face. Within the next week similar lesions appeared on the left hip, right shoulder, both forearms and at the waist. The lesions cracked and bled at times, and progressed in spite of treatment. Because it was thought the lesions were due to arsenic, neoarsphenamine was given in 0.3-Gm. doses.

Examination showed that the lesions were of annular or polycyclic outline with elevated borders, brownish-red in colour. The centres were healing. Scrapings from the border of one of the lesions contained *T. pallidum*. Blood Wassermann and Kahn tests were positive.

The lesions were practically healed after arsphenamine 0.3 Gm  $\times$  3 and bismuth  $\times$  3 given in ten days. After the fifth injection of arsphenamine, only pigmentation marked the sites of the lesions. Reversal of the blood tests was delayed until one year passed, probably because of irregular treatment. Spinal fluid was negative.

**Comment.** In this instance relapse or delayed secondary eruption probably occurred due to inadequate dosage, which was continued because of an erroneous diagnosis of arsenical dermatitis. The skin lesion had some of the characteristics of the tertiary lesion—a secundo-tertiary syphilid. Small dosage, inadequate to kill many treponemata, killed some and permitted sensitization of tissues so that the skin reaction resembled in part some of the characteristics of late skin lesions (Figure 38).

2. The use of small amounts of arsenic may apparently be necessary in some instances because reactions occur when adequate dosage is used. For example, skin reactions or severe gastro-intestinal reactions may occur with 0.6-Gm. doses of neoarsphenamine, but not with 0.45-Gm. doses. Under such circumstances the physician would do well to remember that early in the treatment of acute syphilis, if such a problem presents itself,



FIG 38 Early syphilid resistant to inadequate arsenic dosage (Case 44)

it is far better to change to some other form of trivalent arsenic and to give this in full dosage

3 In a given case the dosage usually adequate for the sex and weight actually may be inadequate This is the type of case in which discussion may arise as to whether the factors involved are an organism of unusual resistance to treatment, or a host deficient in some aspect of its immune reaction The lesions in such a case may be controlled by increasing the

dosage above that usual for the patient on a weight and sex basis (Case 45)

**Case 45.** A twenty-one-year-old single white woman was referred to Dr Edgar Jones (with whom I saw the patient) because of a rash suspected of being of arsenical origin. About seven weeks previously she had consulted a physician because of a maculopapular rash which was intensified after six injections of neoarsphenamine, though the patient was not sure whether it was the same rash or a different one.

Examination at this time revealed a slightly desquamating maculopapular rash on the forearms and thighs. Her weight was 116 lb. Blood Wassermann and Kahn tests were positive.

**Course.** The patient was given mapharsen 0.06 Gm.  $\times$  10. The rash had cleared after the third injection. After a course of bismuth  $\times$  4 a second course of mapharsen 0.04 Gm. was begun. Smaller dosage was used because of nausea. After six such injections, the patient called attention to two symmetrically placed lesions, one on the lateral aspect of each thigh. They were the size of a shilling, purplish red in colour, and presented an irregular nodular surface. Their appearance two months before coincided with the bismuth course. By the use of mapharsen 0.06 Gm. and bismuth simultaneously, and iodides, complete involution of the lesions occurred within three weeks, leaving a pigmented residuum.

**Comment.** This case represents an instance of cutaneous relapse during a course of bismuth and resistance to mapharsen adequate in dosage on a basis of weight and sex. The lesion presented a tertiary like morphology which probably indicates treatment resistance to a dosage inadequate for this particular case.

A word with respect to the morphology of early lesions subjected to insufficient arsenic may be indicated. The manifestations in the secondary stage are of interest since, under the influence of inadequate therapy, there is a tendency for the lesions to assume a form suggestive of, or approaching that of, the syphlid of late syphilis. The lesions may change from the more common papules or maculopapular ones to more infiltrative forms, become fewer in number, and assume annular or serpiginous configuration (Case 44 is a good example of this). That such lesions are not tertiary is shown by the fact that the *T. pallidum* is demonstrable by darkfield examination, and also by the fact that scarring does not take place. It seems probable that inadequacy of treatment, since it does not eradicate infection, nor on the other hand allow natural immunity to develop, permits the development of a sensitivity in the host to the products of the treponema. This "allergy" accounts for a reaction having some of the characteristics of tertiary skin manifestations. The reason for briefly discussing these facts is to warn the physician against jumping to the conclusion that he is dealing with late syphilis upon casual inspection of

these unusual skin lesions. The public-health implications in the recognition of this form of acute syphilis are obvious.

**Summary.** The treatment of the infectious stage of syphilis requires regularity of treatment and full dosage of the trivalent arsenical of choice. If acute lesions are resistant to adequate dosage (Case 54) a change to another arsenical is indicated, and if the disease is not gotten in hand fever therapy may be necessary as an additional therapeutic procedure. If, because of untoward reactions under treatment, inadequate dosage seems necessary, a change to another trivalent arsenical is much better and it must be given in full dosage. The physician also must realize that adequacy of dosage bears relationship to the weight of the patient.

### "WASSERMANN FASTNESS" IN EARLY SYPHILIS

Another phase of treatment resistance is the matter of serologic fastness (See Chapter IV). As was indicated in the discussion of prognosis in acute syphilis, in the great majority of cases the blood tests for syphilis are reversed to negative within ninety days after the introduction of adequate treatment, or almost certainly within the first six months of such time. The Co-operative Clinical Group showed that serologic fastness was more common if treatment was inadequate in certain respects, namely, irregular or intermittent treatment, the use of mercury instead of bismuth, and shortening of the first arsenic course. Relative to the regularity of treatment this group of observers found the following: only 11 per cent of the cases of early syphilis treated continuously remained serologically positive, whereas 37 per cent of those receiving intermittent treatment and 68 per cent of those treated irregularly remained seropositive. I should like to add that inadequacy of dosage in the early treatment of acute syphilis may be accompanied by persistently positive blood tests.

If treatment has been adequate in all respects and the serologic tests remain unchanged, the attending physician should suspect either central-nervous-system invasion (as shown by a positive spinal fluid) or visceral syphilis. The Co-operative Clinical Group found about 40 per cent of cases of asymptomatic neurosyphilis to be seroresistant. Failing to demonstrate either, it must be admitted that the cause is unknown. Under such circumstances it is generally assumed that serologic resistance in early syphilis is indicative of the presence of active foci of infection, or at least persistence of infection. This is borne out by the Co-operative Clinical Group findings of about five times more clinical relapse in cases of seroresistant early syphilis than in those with reversal. Moore and Padgett reported similar findings. Though this is no doubt true, there are some cases of serologic fastness in adequately treated acute syphilis which must signify something other than persistent activity. The reason for saying



this is that some of these cases finally reverse spontaneously when treatment is stopped (This is more commonly true in late latent syphilis) An instance of this appears in the report of Case 46

**Case 46** A twenty nine year-old Negress was admitted to the Syphilis Clinic because of a "sore throat" of three weeks duration About five weeks before admission she noted the onset of generalized aching malaise, and loss of strength. She felt feverish, and remained in bed

Examination showed that the weight was 98 lb The throat revealed edema and slight injection The tonsils were very large There was a generalized marked lymphadenopathy Blood Wassermann and Kahn tests were positive

Treatment led to prompt cure of the pharyngitis In twenty three months the patient received arsphenamine 0.3 Gm  $\times$  14, neoarsphenamine 0.45 Gm  $\times$  23, and bismuth  $\times$  54 The spinal fluid was negative at six months Blood Wassermann and Kahn tests remained persistently positive

The patient then was given a three month rest period at the end of which time the blood was still positive She was therefore given bismuth  $\times$  12 Serologic tests were still positive After a second three month rest period, both blood tests had become doubtful During the succeeding three years the tests were consistently negative

**Comment** This patient with acute syphilis received adequate dosage of arsenic for her weight She missed treatment only two times in twenty three months There was no evidence of central nervous system invasion to account for serologic fastness After cessation of treatment spontaneous reversal of the serologic tests occurred

In cases in which there is a delayed reversal of the blood tests as in those reversing after six months of therapy, we have followed Moore's suggestion of the prolongation of continuous treatment until the blood tests have been negative for one year However, in instances of irreversibility, as in the above case we have arbitrarily treated the patient continuously for two years, and in the third year have used two three month courses of bismuth with intervening three month rest periods Following this, the patients have been placed on probation

## CLINICAL RELAPSE

Following the subsidence of the clinical manifestations of the secondary stage, and especially following inadequate anti syphilitic treatment, active foci of the infection persist A lighting up of a focus gives rise to (1) a recurrence of lesions or (2) their appearance for the first time in another tissue or organ Thus in the first category the patient may experience the reappearance of skin and mucous membrane lesions the lighting up of a previous iritis, or skeletal syphilis Under the second heading, for example, may fall the patient who has had the rash of second

ary syphilis which had subsided but in whom the relapse may be manifested by ocular syphilis, a syphilitic hepatitis, or for the first time clinical neurosyphilis (acute syphilitic meningitis) as a flare-up in previously asymptomatic neurosyphilis

Adequate knowledge concerning relapse is of extreme importance to the physician because of (1) its relationship to inadequate treatment, (2) its infectiousness, (3) the need to recognize clearly such relapse entities as iritis, hepatitis, and acute neurosyphilis for what they are, and (4) for the recognition of mucocutaneous recurrence as a *relapse phenomenon* rather than the overworked diagnosis of "reinfection"

Clinical relapse, or recrudescence, is uncommon in untreated acute syphilis. By far the majority of cases of relapse result from inadequacy of antisyphilitic treatment. This may be due to the patient's irregularity in reporting for treatment or in his voluntary or enforced lapse of treatment. Though the medical profession has no control over these factors, it is responsible for such factors as adequacy of dosage, the use of sufficiently long courses of arsenicals early in the course of treatment, the use of a continuous plan of treatment rather than an intermittent one, and spinal-fluid examination. However, relapse may occur while the patient is receiving adequate therapy (Case 54)

Many physicians are unaware of the frequency of recurrent lesions such as the moist erosions on the genitalia and mucous patches in the mouth, both of which are teeming with *T pallida*. Every patient with acute syphilis who has lapsed treatment should be carefully examined when he reports again for treatment. Careful search for moist lesions of the mouth and the anogenital regions is essential. Contact investigation is indicated in any cases found to have such manifestations. As will appear later in the chapter, knowledge with respect to the time interval within which infectious relapse may occur is essential for the proper understanding of this phase of syphilis

The third point with respect to recognition of relapse lesions should be of interest to the practitioner. It emphasizes the ever-present need for adequate history taking. All too often (though fortunately it is becoming less frequent) the patient has been told by his physician that he is "cured" after a dozen or so injections of neoarsphenamine, the blood test having thereby become reversed. In the patient's mind the clinical relapse occurring some months after cessation of treatment cannot therefore be related to the penile lesion, let us say, of eight months before. This is especially likely to be true in the case of iritis, periostitis and osteitis, hepatitis, or central-nervous-system symptoms or signs. The physician who is superficial in his history taking may miss the background of the presenting clinical picture, especially since the patient may neglect

to tell of his acute syphilis which he thinks of as "cured" Mucocutaneous relapse is more likely to arouse suspicion in both patient and physician. However, the appearance of the manifestations noted above in a relatively young person should bring syphilis to mind as the cause.

**Case 47** A thirty year-old white man was admitted to the Medical Clinic because of a "sore mouth and hurting in the stomach." Five months before he had been admitted to another institution because of a penile lesion and rash. Blood tests were positive. (His wife also had a solitary lesion of the vulva.) The patient received eight intravenous and sixteen intramuscular injections, and then lapsed treatment for six weeks before admission to Vanderbilt University Hospital. Three weeks before admission an ulcer was noted on the upper lip. Ten days before admission he developed epigastric distress, nausea and vomiting. The stools were clay-coloured, the urine was dark. A friend called attention to jaundice five days before admission.

Examination disclosed a temperature of 100°. Jaundice of the skin and sclerae was present. The upper lip was swollen and presented a nonindurated, tender superficial ulcer. The smooth, tender edge of the liver was palpable 3 cm. below the right costal margin. A penile scar was present. Blood Wassermann and Kahn tests were positive. Serum from the lip lesion was positive for *T. pallidum*. Spinal fluid was negative. The icterus index was twenty, bile was present in the urine and absent from the stool.

Treatment given was neoarsphenamine 0.1 Gm., five days later 0.2 Gm., in another five days 0.3 Gm. Within these ten days the icterus index dropped to five, and bile reappeared in the stool. The lip lesion began to heal. In the following eighteen months the patient received neoarsphenamine 0.6 Gm.  $\times$  31, and bismuth  $\times$  18. Treatment was irregular. Reversal of blood tests took place within sixty days from the onset of treatment.

**Comment** This patient presents an example of hepatorecurrence and mucosal relapse occurring within three weeks after lapse of treatment begun for secondary syphilis.

Lastly, a proper understanding of the characteristics of mucocutaneous relapse will remove from the practitioner's mind any misconception he may have relative to the frequency of reinfection. It will become clear to him that, though he may see much relapse in his experience, proven reinfection is a condition he will probably never see in a lifetime of practice.

More space will be given to mucocutaneous relapse than to the other forms of relapse. *Syphilis of the eye as a relapse phenomenon will not differ from the lesions as described under this heading in the last chapter.* The same is true for skeletal or hepatic recrudescence. Neurorecurrence is best considered in the discussion of neurosyphilis in Chapter XII. It is necessary to devote some space to mucocutaneous relapse for several reasons: it is the most frequent form of relapse, it is a highly infectious form of syphilis, and thus it is of importance to the public health officer.

Furthermore, the cutaneous lesions tend to differ somewhat in their morphology from the more common skin syphiloderms of the secondary stage

#### MUCOCUTANEOUS RELAPSE

**Frequency.** It is my personal opinion that we have no definite information as to the actual frequency of mucocutaneous relapse. The patient who is so disinterested in antisyphilitic treatment as to lapse treatment after the involution of his primary or secondary lesions is likely to be as disinterested with respect to relapse lesions. The frequency of mucocutaneous relapse in the Co-operative Clinical Group's collected cases was as follows. Among 5,952 cases of acute syphilis (primary and secondary syphilis), there were 360 cases (6 per cent) of mucocutaneous relapse. At the Vanderbilt University Hospital Syphilis Clinic during the period of time in which the diagnosis of acute syphilis was made 1,837 times, there were 128 cases diagnosed as having relapse phenomena. Of these, 86 cases represented cutaneous recurrences, though some also had mucosal lesions. In 35 the relapsing lesions were limited to the mucosae only. There were seven instances of iritis as recurrent manifestations. Recurrent acute syphilis, therefore, accounted for 6.9 per cent of the cases of acute syphilis. (The cases of neurorecurrence are not included in these figures.)

**Influence of Sex and Race.** Of the 121 mucocutaneous relapse cases, Kern selected 80 for a detailed study, on the basis that the patients either were seen in the stage of original infection in the Vanderbilt University Hospital Clinic or that an adequate history of the acute stage of this infection was given. The influence of sex and race on the incidence of mucocutaneous relapse is not of great significance. The factors influencing the apparent incidence in these respects are greater ease of recognition of genital recurrences in the male than in the female, and the irresponsible attitude of the southern Negro relative to apparently innocuous lesions. Of 80 selected cases 39 per cent were white males, 31 per cent white females, 20 per cent coloured males, and 10 per cent coloured females.

The occurrence of infectious relapse depends upon several important factors. These are the stage of infection in which treatment originally was begun, and the amount and regularity of treatment.

**Incidence.** All authors relate the apparent incidence of relapse to the frequency of early syphilis in the same clinic. (It is obvious that no observer knows what the incidence of relapse has been among his cases which have discontinued treatment.) In the Vanderbilt University Hospital cases the original diagnoses (at the time treatment was first started) were primary syphilis in 42.5 per cent, secondary syphilis in 55 per cent, and early latent syphilis in 2.5 per cent. Since it is not actually known what the incidence of relapse is in syphilis, these figures are

difficult of interpretation. However, on the basis of the 472 primary, 1,237 secondary, and 728 early latent cases of syphilis admitted to our clinic, it would appear that the incidence of relapse is greater in the inadequately treated primary cases than in the secondary ones, and certainly much less in the early latent cases. This bears out the generally accepted idea that the earlier treatment is started in the course of acute syphilis, the greater is the interference with the development of natural immunity.

The relationship of the duration of infection to relapse as described in our clinic by Kern compares in general with that found by the Co-operative Clinical Group. Thus 18.3 per cent of mucocutaneous relapses occurred within the first six months of infection, and an additional 30 per cent in the second six months, bringing the total to 48.3 per cent within the first year. Eighty per cent of the cases had relapsed by the end of the second year. (In the Co-operative Clinical Group's statistics 85 per cent of cases relapsed within the first two years.) Another 10 per cent of our patients relapsed in the third year. The importance of the time relationships here involved will be brought out in a discussion of syphilis and marriage. However, the significance of these figures—that is, potential infectiousness within the first two years of infection in the inadequately treated case—should not be passed without a thought of the implications from a public health viewpoint. Relapse after the fourth or at most the fifth year is rare, though it may occur even later than this, as is shown in Case 48.

**Case 48.** A twenty-two-year-old Negro male entered Vanderbilt University Hospital Clinic on September 11, 1928, with a seronegative, darkfield positive penile lesion of two weeks' duration. He received two weekly injections of 0.4 Gm. of arsphenamine. After a lapse of one month he returned for a third arsphenamine injection. At this time the serologic tests for syphilis were still negative.

He disappeared for fifteen months, and then returned with a recurrence of his penile lesion. No darkfield examination was done on this visit, but the serologic reactions had become positive. He received neoarsphenamine 0.6 Gm. and mercury salicylate on that visit, and failed to return for an interval of five years. On return he had another penile lesion. This time he took four injections of arsphenamine 0.3 Gm. and seven injections of bismuth. One year later he returned with a darkfield positive anal condyloma. The date of this visit was June 11, 1936—seven years and nine months after infection.

**Comment.** Worthy of note are the number of relapses and the duration of time over which these occurred.

**Relationship of Therapy to Relapse.** Of the eighty cases studied by Kern, seventy-two had adequate data with regard to treatment received from which certain deductions could be drawn concerning the relationship

of therapy to relapse. Using the Co-operative Clinical Group's criteria of adequate treatment in acute syphilis (twenty injections each of an arsenical and heavy metal), sixty of the seventy-two cases had inadequate therapy for the first course of treatment. Although, as was indicated above, 80 per cent of the total cases relapsed within the first two years of infection, this same tendency did not appear in those adequately treated. Of twelve cases receiving twenty or more injections of an arsenical and corresponding amount of heavy metal, none relapsed in the first year of infection, one in the second year, four in the third year, and the remaining seven between the third and eighth year. Thus, in adequately treated cases relapse tends to be delayed beyond the average period. Among the seventy-two relapse cases, approximately one-third relapsed within six months and two-thirds within one year of cessation of treatment. Only 17 per cent developed clinical relapse two or more years after treatment was stopped. The Co-operative Clinical Group study showed that 9 per cent of mucocutaneous relapses occurred two years or more after cessation of treatment. Among seventy-two Vanderbilt University Hospital cases of relapse the distribution of amount of treatment was as follows:

18.0 per cent received	1-4 injections of arsenic
34.7 per cent received	5-9 injections of arsenic
23.6 per cent received	10-14 injections of arsenic
7.0 per cent received	15-19 injections of arsenic
16.7 per cent received	20-40 injections of arsenic

We believe that the apparent low incidence of relapse in our patients who received the fewest injections may be due to lack of co-operation in such a group; they would be less likely to return to the clinic because of recurrent lesions. Theoretically a little therapy might interfere less with the development of natural immunity. Likewise the high incidence of relapse in the patients receiving adequate therapy can be explained on the basis of a greater co-operation and probably a better understanding of the seriousness of syphilis as is indicated by the amount of treatment taken. Furthermore, this latter group was also the only one in which the individuals reported regularly for examinations after having been placed on probation. Regularity or irregularity of treatment did not seem to be a factor in the tendency to relapse in the Vanderbilt University Hospital cases in which treatment was inadequate. However, in those receiving more than twenty injections of an arsenical, irregularity seemed to be a factor in seventy-five per cent of the cases.

The preceding discussion has been especially related to inadequacy of treatment. A word is necessary with regard to relapse in cases in which the best routine therapy is being or has been used.

During the routine treatment of acute syphilis, there is one period in which the attending physician should be on the alert for mucocutaneous relapse: during the first course of bismuth. I estimate that a relapse occurs then in about 1-2 per cent of cases. The circumstances will be somewhat as follows: A patient with primary or secondary syphilis has taken weekly injections of an arsenical in adequate dosage for eight to ten weeks. He then begins a four-week course of bismuth. After the second or third bismuth injection he may call attention to mucocutaneous lesions. Or the relapse manifestation may be found by the physician. It is our custom to inspect the mouth and anogenital regions at the end of the first two or three weeks of the first bismuth course, especially if there has been a serorelapse of a previously reversed blood test. An examination will occasionally be rewarded by the finding of an infectious lesion, and such will indicate the need for investigation of intimate contacts. (A practical fact which must be faced is the persistent sexual promiscuity among clinic clientèle, in spite of advice to the contrary.) These facts have led us to advise the overlapping of the first arsenic and bismuth courses as appeared in the treatment schedule in Chapter vii. This scheme permits the attainment of a definite bismuth level in the blood before the arsenic course is completed.

The other fact relative to relapse and adequate therapy is the realization that ideal therapy is not 100 per cent effective. An occasional patient who has reported consistently for treatment and has had full dosage of the antisyphilitic drugs in a continuous régime may suffer relapse. Three such cases occurred in the eighty selected cases of relapse in our clinic. (See Cases 49 and 53.)

**Case 49.** A white male, aged twenty-nine, entered the clinic in May, 1938, with a seropositive, darkfield-positive chancre. He received neoarsphenamine 0.6 Gm.  $\times 34$ , and bismuth salicylate  $\times 36$ . His blood tests became negative in three months and remained consistently so throughout therapy. He was placed on probation toward the end of 1939. He returned in November, 1940, for examination, and was found to have negative Wassermann and Kahn tests and no physical manifestations of syphilis. One month later he returned with a monorecidive on the penis which was darkfield positive. Wassermann and Kahn tests had both reverted to positive.

**Comment.** In spite of adequate treatment, by modern standards, a recurrent chancre appeared within twelve months after therapy was stopped.

**Characteristics of Mucocutaneous Relapse.** Though secondary relapse usually occurs but once, multiple relapses may occur. Among the eighty cases in our clinic, 89 per cent experienced one relapse, 9.6 per cent two relapses, and 1.4 per cent three relapses. (See cases 48, 52, and 55.)

**THE LESIONS OF SECONDARY RELAPSE** These may consist of either skin manifestations or moist erosions or mucous patches of the anogenital region or of the mouth and throat. A comparison of the type and distribution of secondary lesions with the same features of relapse lesions indicates that, if anything, the latter present a greater public-health hazard than the former. The site of the lesions in clinical secondary recurrence in our group was such that 62 per cent of the cases were potentially infectious (This frequency is identical with that found by Stokes, namely, 61 per cent in fifty-six cases.) Among our eighty cases, the recorded physical examination in seventy-seven was satisfactory for an analysis of the sites involved by the mucocutaneous-relapse manifestations. The distribution—very similar to that described by Stokes in fifty-six cases—is shown in Table X.

TABLE X  
SITES OF MUCOCUTANEOUS-RELAPSE LESIONS

Site	Number
Genitalia only	18
Genitalia and buccal mucosa	8
Genitalia and skin	6
Genitalia, buccal mucosa, and skin	4
Buccal mucosa only	6
Buccal mucosa and skin	6
Skin only	29

The monorecitive may be a form which the clinical relapse may assume. This may be described as a recurrent chancre appearing at the site of the original primary lesion (Case 49). All the characteristics of the chancre may be present, even with regional lymphadenopathy. Darkfield examination is positive. As will be pointed out under the discussion of reinfection, the physician may be misled in making a diagnosis of reinfection in this type of case.

Mucous patches of the mucosa of throat, mouth, and lips are identical in appearance with those described under the consideration of secondary syphilis in Chapter VII (Cases 50 and 51). Similarly, the moist erosions of the anogenital region correspond in morphology to those of the active secondary stage of syphilis (Case 52). Condylomata and moist papules of the anogenital areas are the same as those described in the preceding chapter.

**Case 50.** A twenty-three-year-old white male complained of two large, indurated, painless ulcers on the prepuce of three weeks' duration, right inguinal lymphadenitis was present. He had been seronegative three months



before Darkfield examination revealed *T pallidum*. A diagnosis of seropositive primary syphilis was made.

The patient received irregularly bismuth  $\times 3$ , and neoarsphenamine 0.6 Gm.  $\times 10$  in the next fifteen weeks. Then following a two week lapse of treatment, he returned because of "sores" on the tongue. A number of patches varying in size from 4-8 mm. in diameter, and covered with a gray exudate, were present on the dorsum of the tongue. *T pallida* were present.

FIG 39

FIG 40



FIG 39 Secondary relapse—mucous patches (Case 50)

FIG 40 Secondary relapse—mucosal ulcer (Case 51)

**Comment** This offers an example of mucous membrane relapse due to irregular treatment. Response was prompt after two injections of arsphenamine 0.4 Gm (Figure 39).

**Case 51.** A twenty-year-old Negro complained of a sore throat. About nine months previously he had developed a penile lesion which lasted two months. He was found to be seropositive, and was given ten intravenous injections and then lapsed treatment. Two weeks before admission he noted "warts" on the penis, and a sore throat.

Examination revealed a large superficial ulcer involving the surface of the right hard and soft palate. Mucous patches were found on the tonsils and posterior pharyngeal wall. The penis showed condylomata acuminata. Material from the palatal ulcer contained *T pallidum*. Blood Wassermann and Kahn tests were positive.

**Comment** This case is an example of mucous membrane relapse due to

lapse of treatment. It also illustrates confluence of mucosal lesions to form a large superficial ulcer (Figure 40).

**Case 52** A thirty-one-year-old white married man entered the clinic in March, 1939. For twelve days, nine months before, he had a hard, painless, penile lesion with associated inguinal adenopathy. Three weeks before admission he noted a sore in the nostril, a sore throat, sores in his mouth, hoarseness, vertigo, and headache which had persisted.

FIG 41

FIG 42



FIG 41 Secondary relapse—moist genital and papulo ulcerative skin lesions (Case 52)

FIG 42 Secondary relapse—solitary papule (Case 53)

Examination disclosed a few acneform lesions scattered over the body. Red, crusted papules were found on the legs. Crusted lesions at both nostrils extended into the nares. Mucous patches were present on the palate and uvula. A bilateral papilledema was found on examination of the optic fundi. Material from the mucous patches contained *T pallidum*. Blood Wassermann and Kahn tests were positive. Spinal fluid examination showed a positive globulin, 40 cells per cu mm, a positive Wassermann in all dilutions and a 5421000000 mastic curve.

Treatment was very irregular: sixty-eight treatments were given in eighty-four weeks. After a year of irregular treatment he was 'Wassermann fast,' and the spinal fluid showed a trace of globulin, 7 cells per cu mm, positive Wassermann in 1 and 0.5-cc and negative in 0.2-cc dilutions with a flat mastic curve.

He was next seen in June, 1941, because of recurrent skin lesions. Examination showed the presence of a red, macular rash scattered over the body. Superficial ulcers were present on the perineum. Moist superficial ulcers were seen on the glans, at the corona, and on the shaft of the penis. Darkfield study revealed treponemata. Blood Wassermann and Kahn tests were positive. The spinal fluid

study showed a positive globulin, 40 cells per cu mm, positive Wassermann in all dilutions, and a 3321000000 mastic curve

**Comment** If the story is correct, this patient was seen first in the stage of 'delayed' secondaries, or a progressing secondary stage. Acute syphilitic meningitis was present. The rest of the picture is that of cutaneous relapse after inadequate treatment, with neurorelapse as measured by spinal fluid changes (Figure 41)

The cutaneous lesions of relapse often have characteristics which differ in certain respects from those of ordinary secondary syphilis. There is a greater tendency for the skin lesions to be fewer in number than in the secondary stage. Not infrequently only a few papules may be present on the body or only one annular lesion, let us say. Furthermore, in contrast to secondary syphilis, there is a greater tendency to the papular and annular types of lesions rather than to the macular or maculopapular types. Among the eighty cases from our clinic, fifty had skin lesions. Their distribution as to type is shown in Table XI

TABLE XI  
TYPE OF CUTANEOUS-RELAPSE LESIONS

Papular	20 (40%)
Annular	17 (34%)
Maculopapular	7 (14%)
Macular	4 (8%)
Pustular	2 (4%)

(It may be of interest to compare this table with a similar one on secondary syphilis in Chapter VII.)

The papules are usually brownish red in colour, and may be found upon any part of the body. Such lesions may be solitary, as in Case 53. They may be more numerous, as in Case 54, in which the palmar papules developed while under treatment, and were identical with those seen in secondary syphilis.

**Case 53** A forty-two-year-old white bachelor was referred from the Surgical Clinic because of a positive serology. The history and physical examination being negative, a diagnosis of late latent syphilis was made. Without missing a single treatment, he received neoarsphenamine 0.6 Gm  $\times$  26, and bismuth  $\times$  34. Sero-reversal occurred after three months of treatment. Spinal fluid was negative. After three months' probation the blood was still negative.

At the end of six months' probation blood Wassermann and Kahn tests were positive. A small circinate lesion on the inner aspect of the thigh was the only one present, and was thought by him to be due to a salve prescribed for *tinea cruris*. Serum obtained from this lesion contained *T. pallidum*. Spinal fluid was negative.

The patient now admitted that a few months before we first saw him he had not felt well, and since his blood was found positive he received seven intravenous injections. After this he had had some "blisters" on his penis healed by local treatment.

**Comment.** The patient when first seen was thus in early latency. In spite of remarkably regular treatment, and upon adequate dosage, relapse occurred six



FIG 43 Secondary relapse—papular syphilid (Case 54)

months after being placed on probation. A second complete course of treatment was given. If this patient had not been very co-operative, as was shown by clinic attendance and return for re-examinations, it is very possible that this innocuous lesion would have been passed over (Figure 42).

**Case 54.** A thirty-year-old white housewife complained of a sore throat and "falling hair" of three to four weeks' duration. Her husband had secondary syphilis five months previously, and her blood had been examined monthly since then. It was found positive at the time her symptoms began. The patient had received neoarsphenamine 0.3 Gm. at weekly intervals for three weeks before entering the clinic.

Examination was negative. She was found to be seropositive. Treatment was continued with neoarsphenamine 0.6 Gm  $\times 4$  at weekly intervals. She then became aware of palmar lesions. None was found elsewhere. Scrapings from these contained *T. pallidum*. After three injections of mapharsen 0.06 Gm. the lesions had healed. Continuous treatment was carried out.

**Comment.** This is an example of relapse under treatment. It is possible that the inadequate dosage employed before we saw the patient influenced the clinical course of the disease. The case also illustrates the beneficial effect of a change to another arsenical in resistant or relapse cases (Figure 43. The dark palmar papules are those traumatized for serum for darkfield study.)

Annular lesions are found much more commonly among relapse cases than in secondary syphilis. They are of interest since they show, in a way, a transition from the secondary to the tertiary syphilid. The annular type of manifestation is more likely to appear as a relapse phenomenon in patients having had syphilis for quite some time (Case 55). This indicates probably some degree of sensitization to the products of infection. The fact that these relapse lesions outwardly present tertiary features is shown by the rare tendency to become destructive. We have had such an instance in a patient who presented two annular, nodular lesions of the face. The lesions were darkfield positive. On the soles of the feet appeared destructive lesions which appeared as ulcerated tertiary lesions. Inadequacy of treatment had allowed the development of sensitivity to the infection.

Macular and maculopapular lesions are rare, as is indicated above.

**Case 55** A thirty-year-old white housewife was referred from the Gynecology Clinic in February, 1936. She was unaware of the rash which had been noted in that clinic. Her husband had had a penile lesion one month before.

Examination disclosed a faint roseola on the chest and abdomen, and a few maculopapular lesions on the palms. Pharyngitis was present, as well as generalized lymphadenopathy. Blood Wassermann and Kahn tests were positive.

During a period of eighty weeks in 1936-1937, the patient received neosphenamine 0.6 Gm  $\times$  37, and bismuth  $\times$  20. The first seven months of treatment were quite regular. Complete reversal of the Kahn never took place. Spinal fluid examination was negative.

The patient returned in March, 1939, because of a rash of three weeks' duration. (She had been seronegative at another hospital in 1938.) 'Sores' in the mouth and a 'blister' on the genitalia had been noted. Examination showed pigmentation of an involuting rash, and a shallow ulcer on the lower lip. Serum from the latter was positive for *T. pallidum*. Blood tests were positive.

The diagnosis was mucocutaneous relapse, and she was given mapharsen 0.04 Gm  $\times$  8, and bismuth  $\times$  6 in a period of twenty-six weeks. The lesions responded promptly to therapy. Treatment was again lapsed.

She was next seen in April, 1941, because of a rash and sore tongue. Treatment had been continued, so she said, for six months after she lapsed in 1939. Examination revealed copper-coloured annular lesions on the trunk, arms, thighs, palms, and labia majora. There was mucous patch on the tongue, from which *T. pallida* were demonstrated on darkfield examination. Blood Wassermann and Kahn tests were positive.

**Comment** This patient had at least two relapses because of irregularity of treatment (Figure 44).

**Serologic findings in infectious relapse** are worthy of consideration. In the eighty cases of relapse in our clinic, Kern found that fifty-five patients had maintained serologic fastness throughout the treatment period before clinical relapse occurred. There were twenty-one cases in which the blood

Wassermann and Kahn tests became negative under treatment but which relapsed to positive at the time of the clinical relapse. In the remainder (four cases) the serologic tests were not strongly positive at the time of



FIG. 44. Secondary relapse—annular syphilid (Case 55).

relapse. I think it is fair to point out that these four may well represent technical or other errors. (Stokes found two seronegative cases in his group of fifty-six cases. One of these was a monorecitive.) For practical purposes it may be said that the serologic tests for syphilis will be positive in all cases of clinical relapse. If a lesion which might conceivably represent a relapse phenomenon in a known syphilitic patient occurs during the seronegative stage, the attending physician had better search for causes other than syphilis, whether it be in mucous membrane, skin, eye, or central nervous system. Seronegativity must be proven by more than one blood

test It must not be forgotten that the darkfield examination is of great assistance in secondary relapse The *T pallidum* was demonstrated in 75 per cent of the Vanderbilt University Hospital cases in which lesions suitable for darkfield examination were present

**Treatment.** The treatment of relapse is quite obvious The application of the continuous regime of treatment, as in the case of acute syphilis, is necessary Pressure must be put upon the patient to be regular in attendance for treatment Since serologic fastness is not unusual in these cases, it is our plan to proceed with treatment as was indicated earlier in this chapter in the discussion of "Wassermann fastness" The occasional necessity of a change to another arsenical compound arises if clinical relapse occurs during regular treatment, as in Case 54

### SERORELAPSE IN EARLY SYPHILIS

In a relatively small percentage of cases of early syphilis, after ideal treatment has been completed, there may be a recurrence of positive complement-fixation and precipitation tests This will be found most often at from three to twelve months after cessation of treatment If this can occur in well treated cases, the probability of serorelapse obviously is greater in the inadequately treated cases either under the intermittent plan, or under irregularity of treatment Under such circumstances the incidence of serorelapse will be related to the amount and regularity of antisyphilitic treatment It is generally accepted that serorelapse is more likely to occur in those patients in whom reversal took place very early in treatment The explanation of this tendency toward serorelapse is that it represents an index of a lowered immunity response of the host to infection

The question arises, what is the significance of serorelapse in early syphilis? It very likely has a different connotation than serorelapse in late syphilis In early syphilis it probably means a re-activation of infection in some hitherto quiescent focus with a redissemination of organisms In certain cases with serorelapse the alert physician may prove the redissemination of organisms by demonstrating the presence of clinical relapse (Case 53) A careful examination of the patient with serorelapse not infrequently reveals a mucous patch in the mouth, a moist erosion in the anogenital region, or a positive spinal fluid It therefore seems only logical to accept the probability that the occurrence of serorelapse in a patient who has completed treatment for early syphilis means a "flare-up" of the infection And it is possible that clinical relapse actually may have occurred on a mucosal surface not available for examination, or as an evanescent lesion not present at the time of examination Therefore the physician must carefully examine the patient for evidence of clinical relapse, and the spinal fluid must be re-examined Furthermore, it would be the part of

wisdom to examine and keep under observation the persons who have had intimate contact with such a patient

The management of serorelapse is quite obvious if the above statement regarding its significance is correct. It implies that the treatment for acute syphilis must be repeated. However, we have shortened the treatment by one course each of arsenic and bismuth, in some instances where there was no evidence of clinical or neurorelapse, and in which serologic reversal occurred quite promptly. Apparently results have been satisfactory in such instances in that there was no apparent progression in the disease subsequently, and seronegativity was maintained.

## REINFECTION

Reinfection in syphilis implies that biologic cure has occurred. A second infection with the *T. pallidum* is probably one of the rarest occurrences in the field of syphilology. Yet from my contact with practitioners in post-graduate courses I find that it is accepted as being quite common, and that practically all of such physicians have made the diagnosis of reinfection. In the 1,837 cases of primary, secondary, and secondary relapse syphilis which constitute the material of infectious syphilis in the Vanderbilt University Hospital Syphilis Clinic, not a single proven case of reinfection has occurred. During this time there have been a half dozen or so of cases in which reinfection seemed possible, for certain reasons, but the rigid criteria for reinfection could not be met.

Though it admittedly proves nothing, it is a striking fact that our sexually promiscuous patients who have completed treatment for acute syphilis do not return with newly acquired syphilitic lesions. The proof of their consistent sexual exposure is indicated by the commonplace occurrence of gonorrhea, chancroidal infection, and lymphopathia venereum during the years subsequent to the completion of antisyphilitic treatment. Surely if reinfection with syphilis were common, we should encounter at least one such example, for many of our treated syphilitic patients are without a doubt repeatedly exposed to the disease.

It is unquestionably true that the common misconception among the medical profession relative to reinfection is to be explained entirely upon an inadequate knowledge of the characteristics of secondary relapse, and the belief still too common that seronegativity implies cure. These false beliefs emphasize the necessity of a proper understanding of the biology and natural course of the syphilitic infection.

Most of the cases of reinfection described in the literature are not acceptable by present-day criteria. Halley and Wassermann in 1928 analysed 676 cases of presumed reinfections reported in the literature. They found 229 of these to be acceptable. The Co-operative Clinical Group in



1931 found, among 5,952 early cases, 40 instances of supposed reinfections. In this same group of early cases there were 360 of mucocutaneous relapse. The Group found that 91 per cent of the relapse cases occurred within the first two years after the cessation of treatment, and that 85 per cent occurred within the first two years of the disease. Also they pointed out that the incidence of mucocutaneous relapse was less after the patient had received 0.15 injections of an arsenical. An analysis of the 40 supposed reinfections revealed that 21 occurred within the first two years of the first infection. Of the rest, eight occurred in the third year, five in the fourth year, and the remaining six cases were distributed as one or two in each of the years up to ten years.

The significance of the high frequency of supposed reinfection—that is, 75 per cent within the first three years after the original infection—is exceedingly pertinent if these facts are viewed in light of the time relationships which characterize clinical relapse. If these were all reinfections it would be difficult to explain this odd and high incidence within the first

TABLE XII

CRITERIA OF REINFECTION (MODIFIED FROM THE CO-OPERATIVE CLINICAL GROUP)<sup>1</sup>

<i>Probable Reinfection</i>	<i>Possible Reinfection</i>
1 Indisputable first infection	1 Indisputable first infection.
2 Clinically and serologically negative for one year after treatment	2 Second chancre different site from first
3 Second chancre in (a) different site, (b) different lymph drainage from first	3 Second chancre characteristic appearance
4 No signs of activity at site of first chancre	4 Positive darkfield second chancre
5 Positive darkfield on second chancre	5 Second chancre must appear at an interval after antisyphilitic treatment
6 Satellite adenopathy present, second chancre	
7 If blood Wassermann reaction becomes positive under observation or—	
8 If a secondary eruption appears at the proper interval laxity will be allowed in items 2, 3b and 6	

<sup>1</sup> From Ven. D. s. Inform.

two or three years subsequent to the first infection with syphilis. Why should not the cases of reinfection with syphilis be scattered over

many years, as would be those of gonorrheal, chancroidal, and lymphopathia venereum infection? To me it means that these supposed cases of reinfection constituted, certainly in most instances, clinical relapse. Of further significance is the fact that of the forty "reinfections" of the Co-operative Clinical Group, 60 per cent had had inadequate treatment and 48 per cent little arsenic and heavy metal. If reinfection presupposes a biologic cure, the fact that 60 per cent of "reinfections" occurred in inadequately treated cases is contrary to our present-day knowledge of the biology and treatment of syphilis.

The Co-operative Clinical Group has set up the tables of criteria for the diagnosis of reinfection. These have been classified as "indisputable," "probable," and "possible." Since none of their cases nor any of those of Halley and Wassermann can be classified as indisputable, I do not believe that the inclusion of this long table of criteria would serve any good purpose in this book. Therefore only the criteria for "probable" and "possible" reinfections are included. (See Table XII.)

On the basis of these criteria, the Co-operative Clinical Group classified their cases and those Halley and Wassermann collected from the literature as shown in Table XIII.

TABLE XIII  
REALIGNMENT OF REINFECTIONS BY CO-OPERATIVE CLINICAL  
GROUP CRITERIA<sup>1</sup>

	<i>C C G</i>	<i>Halley and Wasserman</i>
	<i>40 cases</i>	<i>236 cases</i>
Indisputable	0	0
Probable	9	116
Possible	31	120

<sup>1</sup> From Ven Dis Inform

The reasons for the criteria are quite obvious. An indisputable first infection is essential. We have seen patients with primary lesions who have given a history of antisyphilitic treatment some years before. But the basis for the previous diagnosis of syphilis has been extremely questionable in such cases. Usually it has been clinical, and treatment has been given on the basis of a genital lesion without confirmation by darkfield or serologic tests. Or in other cases treatment has been given without clinical symptoms and signs on the report of one positive blood test. We know that many patients are classed as having syphilis on a doubtful or a biologically false positive precipitation test. Therefore the *proof* of the first infection must be established.

A negative physical examination and negative spinal fluid and blood tests for syphilis during one to two years following cessation of treatment are essential for a diagnosis of reinfection in light of the frequency of relapse in this period of time. Because the monorecursive recurrent chancre at the site of the first one is a relapse phenomenon, it is essential that the second chancre be at a different site than the first with an entirely different lymph drainage. A satellite adenitis must be present, since this is rarely present in secondary relapse. Also the reinfection chancre must be seen in the *seronegative, darkfield-positive stage*. The subsequent development of a positive blood test for syphilis and secondary lesions may then offer proof for reinfection. For practical purposes a lesion in a seropositive stage can never be accepted as the lesion of reinfection. Therapy for the first infection must have been adequate, for experience has shown that the inadequately treated case probably never obtains a biologic cure.

In summary it may be said that indisputable reinfection is of extreme rarity. Further, it may be added that the average practitioner will never see even a *probable reinfection*. If the physician, faced with the possibility of reinfection in a given patient, will analyse the background of the presumed first infection, and the circumstances and details of the present infectious lesion, he will, I feel sure, come to the inevitable conclusion that he is dealing with clinical relapse.

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## IX

### LATENT SYPHILIS

AS WAS INDICATED in Chapter II, in the natural course of the syphilitic infection a spontaneous remission of clinical manifestations generally occurs after the acute phase of the disease has passed. Usually the period which follows the acute stage and precedes the appearance of late manifestations is characterized by clinical quiescence. This period is spoken of as clinical latency, or the stage of latent syphilis\*. It must be clearly understood that this does not imply inactivity or lack of progression of the disease.

It would be of great value if the prognosis in untreated syphilis were accurately known. As was indicated in Chapter II, this is not known, and probably never will be known in these days of more or less universal treatment of the disease. Figures indicating the prevalence of latency among hospital or clinic patients are misleading since they represent a selected group. The selection is such that the percentage of latent cases will be smaller than it should be. A greater number of cases of clinical syphilis will be represented in such groups than would be found in surveys of the population at large.

The only group of cases giving us some inkling as to what may be expected in the natural course of the untreated disease is the much-publicized study of Bruusgaard. Even this group of cases is selected, and Sowder recently has done a great service in calling attention to this selection. However, this study serves to give some clue, even though not accurate, as to the course of syphilis.

To review briefly the background of Bruusgaard's study, I will draw freely from Sowder's paper. Before the introduction of arsenic into the treatment of acute syphilis, Boeck, of Oslo, felt that the antisyphilitic treatment of his day was of no avail. Therefore, from 1891 to 1910, 2,181 cases of acute syphilis admitted to his clinic were given no treatment (These, in most instances, were diagnosed clinically since most of this period antedated the days of the laboratory diagnosis of syphilis).

In 1925 Bruusgaard, Boeck's successor, attempted a follow-up study of these untreated cases. The patients had had syphilis for from fifteen to forty years. Clinic and hospital visits, autopsy records, and death certificates were used in getting together information on these cases. Of the

\* *Serologic latency* is the state in which clinical syphilis may be progressing but in which the serologic tests for syphilis are negative. This occurs especially in cardiovascular syphilis, and in certain types of central nervous system syphilis. *Pathologic latency* is the state in which no apparent inflammatory reaction can be demonstrated by the pathologist.

original group of cases, four hundred and seventy-three or one-fifth of the total provided some information

Bruusgaard pointed out that the patients who were followed through clinic or hospital records had presented themselves because of symptoms of some type. Thus the symptomless group was not properly represented in the study. Furthermore, in the group which was followed there were many women. Those in the child-bearing age, who gave birth to syphilitic children, were available for follow-up evaluation. Those with normal children did not have the same representation in the study.

The neurosyphilitics also represented a selected group, for one method of finding Boeck's original cases was to search the records of the Norwegian insane asylums. Bruusgaard pointed out that most patients with general paresis will need institutional treatment. Since only thirteen such people were found, out of the original 2,181 cases it was shown that this late manifestation occurred but rarely.

With respect to cardiovascular syphilis Bruusgaard's figures are weighted in favour of syphilis as the cause of heart disease, since, if cardiac or vascular death was recorded among these cases, it was accepted as being on the basis of syphilis. Obviously this is incorrect, since patients with latent syphilis may die of cardiovascular disease due to causes other than syphilis.

Sowder also indicates that the inclusion of the dead group in the study weights the statistics with respect to the seriousness of syphilis since there will be a higher incidence of the serious lesions in the dead group. As this author points out, the selection in Bruusgaard's material was such as to exaggerate the gravity of the disease.

In spite of these observations it seems probable that Bruusgaard's findings will be the only ones ever available to give at least an approximate idea of what may be expected in untreated syphilis. Therefore Table XIV, modified from several in Bruusgaard's paper, is included in this discussion. This table covers the three hundred and nine living patients. The final examination included a thorough physical examination, especially with respect to the cardiovascular and central nervous systems. Roentgenologic examination of the heart was carried out. Serologic tests on the blood were usually done. Spinal fluid examination unfortunately was not done frequently.

Of one hundred and sixty-four patients who died, necropsy was done in forty. Cardiovascular disease was the cause of death in forty-three or 26.2 per cent of cases. Bruusgaard admits that many of these were probably due to cardiovascular disease other than syphilitic. Death due to *tuberculosis dorsalis* or general paresis occurred in only five instances, or 3 per cent. All other deaths were presumably due to nonsyphilitic causes.

TABLE XIV  
STATUS OF SYPHILIS IN UNTREATED PATIENTS AT TIME OF "FOLLOW-UP"  
EXAMINATION (MODIFIED FROM BRUGSGAARD'S TABLES)

Status of Syphilis in Patient at Time of Final Examination	Interval in Years Between Infection and Final Examination							
	3-10 yrs.		10-20 yrs.		20-30 yrs.		30-40 yrs.	
	M.	F.	M.	F.	M.	F.	M.	F.
Cardiovascular syphilis . . .	—	—	—	1	7	3	7	1
Neurosyphilis . . .	2	2	3	8	3	6	6	2
Tertiary syphilis (skin, bone, mucosa)	6	21	5	16	1	7	—	2
W <sub>2</sub> R <sub>1</sub> positive—symptomatic . .	—	29	5	4	7	12	6	5
W <sub>2</sub> R <sub>1</sub> positive—asymptomatic . .	6	13	10	14	28	26	20	15
W <sub>2</sub> R <sub>1</sub> negative—symptomatic . .	—	—	—	—	—	—	—	—
W <sub>2</sub> R <sub>1</sub> negative—asymptomatic . .	—	—	—	—	—	—	—	—
Total by sex . . .	14	65	23	43	—	51	39	25
Total both sexes . . .	79		66		100		64	

1 "W<sub>2</sub>R<sub>1</sub>" means Wassermann reaction on the blood.

In 1936 Vonderlehr and his collaborators made a study of untreated syphilis in Negro males. The study was conducted in a rural county of a Southern state, and involved Negro males of twenty five or more years of age. These investigators compared the morbidity in three hundred and ninety nine of the seropositive Negroes who gave a history of infection with two hundred and one presumably nonsyphilitic males. Their findings are in disagreement with those of Bruusgaard, if we may accept the diseases listed by them as being of syphilitic etiology. A high incidence of cardiovascular disease was noted. However, as the authors of this study seem to realize, a question may be raised as to the possible importance of hypertension and arteriosclerosis in the pathogenesis of cardiovascular disease in the syphilitic Negro male. Of the three hundred and ninety nine untreated cases, 7.8 per cent had clinical evidence of central nervous system disease, 18.3 per cent had asymptomatic neurosyphilis, 9 per cent had syphilis of the bones or joints, less than 1 per cent had syphilis of the skin, and 2 per cent had a combination of syphilis of the skin and bone.

## DEFINITION

**Clinical Latency** It may be said that clinical latency is the stage during which the syphilitic infection gives no clinical manifestations, in other words, the signs of infection are below the clinical horizon, as was shown in the graphic representation of the natural course of the infection in Chapter II. Such symptomless infection can be diagnosed only on a history of syphilis, the serologic tests for syphilis, and on some of the residua of previous syphilitic lesions (certain types of cutaneous scars, central nervous system findings, and the like). *A diagnosis of latency implies that the spinal fluid has been examined and that it is negative.* A diagnosis of asymptomatic *neurosyphilis* has a different connotation than that of latent syphilis. It will be shown in the chapter on neurosyphilis that in an asymptomatic case the attendant prognosis is much different than in a latent case.

## PATHOLOGY

A certain percentage of the bodies of asymptomatic syphilitic patients when examined at the necropsy table will show evidence of a progressing syphilitic inflammatory process. Warthin was greatly interested in the pathologic demonstration of syphilitic lesions. Some students of the disease and many pathologists feel that he read syphilis into inflammatory reactions which were probably not syphilitic. In 1931 Warthin reported upon the frequency of syphilis as diagnosed by him on microscopic study

of autopsy material. Among 1,675 cases, he found evidence of syphilis in four hundred and eight men and eighty-six women. His classification of all these cases as latent is incorrect, since he includes instances of gummata and aneurysms. The pathologic diagnosis of syphilis was made in 43.7 per cent of the cases from 1909-1919, and in 25.7 per cent of those from 1919-1929. Microscopic evidence of syphilis was found in the spinal cord, brain, meninges, aorta, myocardium, liver, adrenals, pancreas, and testes. He found the liver to be least frequently involved (27.8 per cent), and the aorta to be most frequently affected (97.6 per cent) in those having the pathologic diagnosis of syphilis. A criticism of Warthin's figures made at times is that he did not give consideration to the antemortem diagnosis of syphilis in cases so diagnosed at necropsy. He merely stated that the "presumptive" Kahn test checked some of his cases very closely.

In a period of twelve years at Vanderbilt University Hospital, necropsies had been done on one hundred and sixty-six syphilitic patients over fifteen years of age. All were probably patients with acquired syphilis. The cases were accepted as being syphilitic on the basis of (1) the pathologic diagnosis of syphilis, (2) a positive Wassermann or Kahn test on blood or spinal fluid, and (3) a satisfactory history of syphilis either with or without treatment. Tables XV and XVI relate the pathologic evidence of syphilis to race, sex, and serologic findings.

TABLE XV

DISTRIBUTION OF SYPHILITIC PATIENTS COMING TO NECROPSY,  
BY RACE AND SEX

	<i>Diagnosis of Syphilis</i>		
	<i>Clinical or Serologic Diagnosis</i>		
<i>Race and Sex</i>	<i>Pathologic</i>	<i>(No Pathologic Evidence)</i>	<i>Totals</i>
White males	28	16	44
White females	5	7	12
Coloured males	49	25	74
Coloured females	16	20	36
	—	—	—
Totals	98	68	166



TABLE XVI

SEROLOGIC FINDINGS IN SYPHILITIC PATIENTS COMING TO NECROPSY

Serologic Findings	Diagnosis of Syphilis		Totals
	Clinical or Serologic Diagnosis Pathologic	(No Pathologic Evidence)	
Blood			
Wassermann or Kahn positive	56	50	106
Spinal fluid positive	4	—	4
Spinal fluid positive and WaR or Kahn positive in the blood	15	6	21
Serologic tests negative	23	12	35
	—	—	—
Totals	98	68	166

Obviously it would be unfair to imply that these figures give an accurate picture as to the frequency of pathologic evidence of syphilis in latent cases. This group of one hundred and sixty six cases does *not* represent latent syphilis only. In the majority of the ninety-eight cases having pathologic findings of syphilis, lesions were present which were clinically recognizable—forty two, for example, had either aortic insufficiency and aortic aneurysm or both, eleven had recognizable central nervous-system syphilis, several had tertiary skin lesions or gumma of the pharynx. The figures are of interest in showing that 40.7 per cent of one hundred and sixty six syphilitics dying in a general hospital had no pathologic evidence of syphilis, and that about one fifth of the cases were seronegative.

## INCIDENCE

It is difficult to speak of the incidence of latent syphilis since it may represent merely an intermediary stage between acute syphilis and one of the manifestations of late syphilis. In such a case there may be latency to-day and tertiary syphilis a month later. On the other hand latency (untreated) may be permanent, spanning the time from the disappearance of the primary or secondary lesions, as the case may be, to the patient's death fifty years later of, say, carcinoma, degenerative heart disease, or pneumonia. Incidence as a term may be used only in setting forth the number of cases that are admitted to a clinic or hospital in the *apparent* stage of latency. It is generally said that in the average syphilis clinic about 50 per cent of the patients are admitted in the latent stage.

TABLE XVII

DISTRIBUTION OF PATIENTS WITH EARLY AND LATE SYPHILIS  
BY RACE AND SEX<sup>1</sup>

<i>Race and Sex</i>	<i>Early</i>	<i>Late</i>	<i>Totals</i>
White males	119	189	308
White females	159	233	392
Coloured males	207	311	518
Coloured females	243	919	1,162
<b>Totals</b>	<b>728</b>	<b>1,652</b>	<b>2,380</b>

<sup>1</sup> As will appear below I prefer to classify latent syphilis of less than four years as early and that of more than this time as late. However, since Moore's diagnostic scheme has been used in our clinic for years, the distribution of patients into early and late in this table is on the basis of two rather than four years.

Of 6,259 cases of syphilis admitted to the Vanderbilt University Hospital Syphilis Clinic, the number diagnosed as latent was 2,380 (38 per cent). These figures are only approximate, for in the early days of the clinic more patients failed to have a spinal fluid examination than in later years. Therefore, some instances of asymptomatic neurosyphilis were included in the group. The preceding Table XVII illustrates the distribution of the 2,380 cases of latent syphilis with respect to their classification as early or late. It reveals that the diagnosis of late latency was twice as frequent as that of early latency. Two thirds of the patients diagnosed as being in the latent stage of syphilis were women.

## DIAGNOSIS

The frequency of the diagnosis of latent syphilis varies in inverse ratio with the diagnostic acumen and clinical experience of the observer. In other words, the more searching the examination is, the more often clinical signs of active syphilis will be found, and the less frequent will be the diagnosis of latent syphilis.

*The spinal fluid must be shown to be negative before the diagnosis of latency can be established.* Therefore, the spinal fluid examination is an imperative part of the examination in the apparently latent case of syphilis. The establishment of the diagnosis of latent syphilis includes a careful history with respect to the acute phases of syphilis, a history of miscarriages or stillbirths, or the birth of congenitally syphilitic children. Most diagnoses of latent syphilis are made on serologic findings. The proper interpretation of these tests has been taken up in Chapter IV. Again, however, I wish to point out the grave responsibility which the physician assumes in the

diagnosis of syphilis on serologic findings without collateral evidence. This is especially true in tests not consistently or strongly positive.

Latent cases are commonly divided into early and late. From a clinical viewpoint the division between these two is based on a limit of four years. Thus in cases where the evidence points to syphilis of less than four years' duration the case should be classified as early latent. Those of more than four years should be classified as late latent. In many instances the duration of infection cannot be ascertained and the cases hence must be classified as of unknown duration. For administrative reasons in public-health activities the age of the patient is commonly used for classification purposes. That is, patients under twenty-five years of age are considered to be early latent, and those over that age late latent. This is unfortunate, for it tends to cause inaccurate thinking in epidemiologic work. In our clinic, the acute cases occurring above this arbitrary age limit make up a respectable number.

The four-year period as a dividing point between early and late latency has not been chosen for arbitrary reasons, but on the basis of certain important facts. This time interval delimits approximately the period of potential infectiousness. Thus for practical purposes mucocutaneous relapse occurs within this period. (Only rarely does it occur later.) Just as this period encompasses practically all infectious relapses, so it also includes practically all neurorecurrences. If the central nervous system has escaped invasion during the first four years of infection, the chance of its being invaded later is very small.

So that there may be no misunderstanding on the part of the reader, it should be noted that another classification of early latency exists—infection of two years or less. This is used in public-health literature. The basis for the use of this period is the fact that about 85 per cent of infectious relapses occur within two years of infection. From a public health viewpoint the acceptance of a two-year period as the dividing line between early and late latency is logical. Since contact investigation and follow-up cannot be universal, it would seem wiser, as regards the syphilis-control programme, to concentrate all effort upon syphilis of two years' or less duration. From a consideration of expenditure of effort and money in syphilis control, I am in agreement with this viewpoint. But from the standpoint of clinical syphilis and the natural course of the infection, the reader must think in terms of the four-year time period as the borderline between early and late latency.

The examination of the patient with latent syphilis should be thorough, but the emphasis on certain details of the examination may be different in the early as compared to the late case.

In the presence of syphilis of less than four years' duration, especially if

inadequately treated, the search for infectious lesions should be meticulous (see Chapter viii) Thus the oral and pharyngeal mucous membranes must be carefully inspected The skin must be examined for relapse lesions Diligent search should be made for moist erosions, papules, and fissures of the anogenital regions, all of which are infectious if of syphilitic origin The finding of any of these lesions is a cause for investigation of the patient's intimate contacts In the married person this means the examination of the marital partner and the children, if any, as well as any extramarital sex contacts By placing emphasis upon the search for evidence of infectious relapse, I do not imply that the examination should be done without thought of possible precocious tertiaryism

Late latency presents a different problem in examination and diagnosis than does early latency This is especially true the later the examination is made after the date of infection Thus with the passage of time beyond the four-year period, the possibility of infectious relapse becomes more improbable, and finally impossible The study of the patient then should be made with an attempt at the demonstration of tertiary manifestations of syphilis Thus search is made for evidence of late benign lesions, or cardiovascular syphilis and central nervous system syphilis, all of which will be discussed in subsequent chapters A careful history and physical examination (see Chapter iii), the use of roentgenograms wherever indicated, and spinal fluid examination are imperative Examination of the marital partner and children is indicated The sexual contact of the patient who has had syphilis of more than four year's duration is in no danger of acquiring the disease (This statement uses the period four years advisedly, with recognition of an occasional relapse in the fifth, sixth, or seventh year) It is a common misconception among physicians that a syphilitic patient is infectious for years, and even decades For example, some of our postgraduate students have doubted the need for inquiry as to extramarital exposure, and the necessity of contact investigation in the patient with acute syphilis whose spouse has had syphilis for a decade or so These physicians were willing to believe that the recent infection must have been acquired from the syphilitic marital partner

The serologic test for syphilis will be strongly positive in the untreated early latent case As was pointed out in the chapter on serologic diagnosis, one should question a diagnosis of syphilis in an untreated patient who had a genital lesion two or three years before, and now has a doubtful blood test It must be recognized, however, that with the passage of years, usually many years, spontaneous reversal of the blood may occur Instead of complete reversal, either the complement fixation test or the flocculation test may become negative, the other remaining positive, or the reagin content may vary so that the results of the tests may fluctuate from nega-

tive, through doubtful, to positive at times. If the diagnosis of latent syphilis is made upon the serologic tests alone, it should never be done upon one test only. *In the absence of a good confirmatory history of syphilis, or previous properly done tests, insist on two strongly positive tests before accepting the diagnosis of latent syphilis.*

## TREATMENT

### EARLY LATENT SYPHILIS

The objective of treatment in the early latent case is (1) to attempt to obtain a "cure," clinical as well as serologic, and (2) to prevent infectious relapse. For all intents and purposes, the treatment of this disease in the first two years of the infection should be that of acute syphilis (see Chapter vii). This is true with few exceptions, irrespective of age or general physical state. The spinal-fluid examination may need to be repeated at the end of the treatment course if treatment has been irregular or if blood tests have not reversed within the usual time (Chapter viii). The patient should be seen periodically for examination, as has been indicated in the discussion of treatment of acute syphilis.

### LATE LATENT SYPHILIS

In asymptomatic syphilis of some years' duration factors other than a positive serologic test may need consideration. Someone has aptly said with fine irony that "syphilis is no longer a disease, but a serologic reaction." Certainly with asymptomatic syphilis of many years' duration, the physician should hesitate before reaching for the syringe filled with neoarsphenamine, and ask himself—should this patient be treated?

For the proper answer to this question the physician must be familiar with the biology, the pathology, and the natural course of the syphilitic infection. As long as the practitioner believes that the syphilitic patient is infectious throughout his life, and that the disease leads inevitably to death, he will be moved to institute treatment at the moment the report of a positive blood test is received.

Our aim in postgraduate teaching for the general practitioner and health officer constantly has been to emphasize that late syphilis is rarely, and certainly *late latent syphilis is never an emergency*. Our instruction has been that the physician should establish the diagnosis without doubt, take stock of the status of the infection in the patient, his physical condition and other factors, and only then plan the therapeutic attack, if any. The physician may well ask himself whether, with a patient in whom the parasite-host relationships apparently have been so amiable, it is wise to disturb this balance by treatment. Might treatment activate a dormant process? In

the following discussion of the treatment of late latent syphilis I would urge the reader to have in mind the natural course of the disease, as discussed in Chapter II. Individualization of the therapeutic management of the late latent patient is imperative.

**Contraindications** Treatment *may not* be indicated for the following reasons

1 **THE PATIENT'S AGE** may contraindicate treatment, though this is related in a way to the matter to be considered in the next paragraph. As Morgan puts it, "A man seventy years old who has had syphilis a half century and has only a positive blood test to show for it is to be congratulated, not treated." The management in such an extreme case is quite clear-cut, but even infection of shorter duration in the aged patient may best not be treated. In an aged patient with a history of syphilis, a positive blood test, and a negative physical examination and spinal fluid, the need for antisyphilitic treatment may be questioned. The physician must weigh the possible harm that syphilis of twenty-five to thirty years' duration might do, against the possible harm of the treatment itself, to the patient's immediate health and his life expectancy.

2 **DURATION OF INFECTION** Syphilitic infection may be of such long duration that the likelihood of the appearance of late lesions is practically nil. In Chapter II it was indicated that the three decades after infection will encompass the clinical manifestations of syphilis in almost all cases. Occasionally one may see tertiary skin lesions beyond this time. Clinical cardiovascular syphilis thirty years after infection is rare. (Paresis and tabes dorsalis may be seen in the years beyond this time, but since we are discussing latent syphilis it is implied that the spinal fluid is negative.) Thus in infections of three decades' duration there is doubt as to whether treatment is indicated. The factor of age may logically be related to that of duration of infection. In infection of two to three decades' duration, in an otherwise healthy person of forty-five to fifty-five years of age, treatment should be conservative, if, under such circumstances, the patient's age is sixty to seventy-five years, no treatment should be given. The institution of treatment in various age groups as related to the duration of infection in the last analysis is a matter of judgment for the physician. Obviously it is utterly impossible to set up a scheme of indications for treatment in late latent syphilis into which all cases can be fitted.

3 **COMPLICATING DISEASE** may interdict antisyphilitic treatment even if syphilis is of less than twenty-five or thirty years' duration. If the patient with latent syphilis is suffering from such serious disease that his days seem numbered, there is no excuse for antisyphilitic treatment. In the patient with inoperable carcinoma, with chronic nephritis and uremia, with advanced heart failure due to hypertensive or arteriosclerotic heart

disease, or with malignant hypertension, and in the patient with far advanced pulmonary tuberculosis, the question which presents itself is—why not allow the patient to spend his last days in peace? This practical problem comes up constantly in a clinic caring for even a moderate sized clientele. Our judgment may be wrong at times in making a decision not to give antisyphilitic treatment in a given case. Within the past few years I can recall two patients who were not treated for latent syphilis because of advanced cardiac failure and inoperable carcinoma of the breast, respectively. In both instances tertiary skin lesions developed. But these are unusual instances and I cite them to indicate that even such occasional experiences do not change my point of view in this matter.

**Indications** Treatment is indicated under the following circumstances

1 **COMPARATIVE YOUTH OF THE PATIENT** may demand that treatment be given. Though syphilis of twenty five or thirty years' duration should not be treated in a patient seventy years of age, it probably should be treated in an otherwise healthy person of forty five to fifty five years of age because of the greater life expectancy.

2 **INFECTION OF RELATIVELY SHORT DURATION** demands treatment irrespective of age, and often in spite of complicating disease. If, from the public health viewpoint, syphilis in a given case requires treatment, it should be treated irrespective of seemingly contraindicating factors, unless these are of such nature that antisyphilitic treatment would be hazardous to life. Therefore syphilis of a few years' duration must be treated even though the patient be seventy five years of age. This is especially true if a little treatment was given at the time of the acute infection, because of the danger of subsequent infectious relapse. The same may be true even in the presence of disease with certain fatal outcome. In general, it is our belief that a patient with syphilis up to twenty years' duration should be treated except in very old age or in the presence of disease in which early death is anticipated.

3 **PREGNANCY IN SYPHILITIC WOMEN** always demands antisyphilitic treatment, with but few exceptions. Since the years involved are those of sexual activity, infections of much over twenty years' duration will usually not be found in the pregnant group.

From the preceding paragraphs it is apparent that it is impossible to set up a regime for every patient with late latent syphilis. This is true not only with regard to late latency, but for all late manifestations of syphilis. A physician should not be an automaton who does "thus and so" because of certain positive findings. No hard and fast rule is set up as to the management of patients with heart disease, peptic ulcer, and the like. Nor is every patient with cholelithiasis or benign prostatic hypertrophy to be treated like every other case, no consideration being taken of age,

general physical condition, and the general operative risk. In the same way, individualization is the keynote in the treatment of the late stages of syphilis. Here at least, something is left to the physician's judgment and experience with respect to the management of the patient. I believe that the good, scientific, experienced general practitioner is a better doctor for such a patient than the syphilologist with his narrow horizon. The experienced, well trained general practitioner has a more sound basic idea of the human being's reaction to disease and treatment. It is to be noted that I said the practitioner must be scientific. The physician who is unfamiliar with the biology of syphilis, its natural course, and its pathology has not the qualifications to be included within the group of which I am speaking.

In view of the foregoing discussion it is apparent that there may be differing opinions with respect to the management of late latent as well as late syphilis. Furthermore, the evaluation of the end results of treatment in much late and late latent syphilis cannot be accurate and unquestioned. These stages are usually found in older individuals and involve such intangible things as host-parasite relationships. Therefore, though I do not decry the invaluable contribution of the Co-operative Clinical Group in pointing the way in the general management of syphilis, I am nevertheless sure that the last word has not been said with respect to the management of the late latent syphilitic patient.

Before it is decided that antisyphilitic treatment should be given in the late latent case, the question arises—what is the objective of such treatment? The physician familiar with the natural course of the disease will not expect a cure in its biological sense when infection has been established for more than two or four years. Such an occurrence would need to be accredited to the host's immune mechanism, and not to the treatment. However, if the physician will visualize the scattered foci of syphilitic inflammation, such as will be described in subsequent chapters, in the wall of the aorta, in bone, skin, liver, etc., he will understand what treatment may accomplish.

The hoped-for effect of treatment is an involution of these scattered foci and their replacement by fibrous scar. How much treatment is necessary, and for how long, is as yet an unanswered question. The only clue to this question is to be had from the Co-operative Clinical Group studies. According to their figures, one can hope to reduce the subsequent occurrence of late lesions of syphilis to approximately 5 per cent by the use of conservative treatment. All we should do is to approximate this amount of treatment and then stop, irrespective of whatever the serologic reactions may be.

Since the objective of treatment is to obtain an involution of probable



miliary gummata and vascular lesions, *the main emphasis should be placed on the use of heavy metal and iodides*. The arsenical drugs should be limited in dosage and to those forms which offer the least possible danger. This is especially true since so many of the patients fall into the older age groups and often have attendant degenerative diseases. Treatment once begun should be continued, for it may be unwise to stir up dormant foci (a theoretical possibility) and then cease treatment. After a prolonged period of continuous treatment rest periods from treatment may be given.

The Jarisch Herxheimer reaction was discussed in Chapter v. In the late lesions of syphilis, which often involve vital structures, the effect of a Herxheimer reaction may be unfortunate and even fatal. An accentuation of the inflammatory reaction at a syphilitic focus may lead to edema of vital tissues, or rupture of structures, such as the aorta, for example. The use of heavy metal and iodides leads to a slower resolution of tertiary lesions with less inflammatory reaction and thus less tissue destruction than do the arsenicals. Even though a diagnosis of latency may be made, knowledge of the syphilitic process makes us realize that there may be inflammatory foci in the wall of the aorta, in the larynx, etc.

**Introductory Medication** With this in mind, *bismuth and iodides* should be the introductory form of medication in presumed late latency. The use of bismuth occasionally may be associated with a Herxheimer reaction, but it is certain to be milder than that due to arsenic (Case 8). Therefore in late latent syphilis bismuth salicylate in oil is given weekly for three to four weeks before any arsenical is used. Potassium iodide may be given by mouth during this period of time to assist in the resolution of granulomatous lesions. It is probable that such a period of preparation will have caused sufficient involution in any lesions which may have been present so that the use of arsenic will not cause a severe Herxheimer reaction. However, if there is anything about a given case to suggest possible cardiovascular involvement, it is better to use bismuth for a period of six to ten weeks. Three weeks of bismuth may be insufficient to prevent a Herxheimer reaction.

**Subsequent Medication** Subsequent to the introductory course of bismuth, *arsenic therapy* may be used. This should consist of neoarsphenamine or arsenoxide. Though it is not known whether the latter is as effective as neoarsphenamine in late syphilis, I prefer to use it in aged persons as its use is associated with the fewest reactions. Continuous treatment consisting of alternating courses of arsenic and bismuth is given until the patient has received twenty-four injections of arsenic and thirty-three to thirty-six injections of bismuth. Following such a scheme, at times it seems best to add three months of rest to be followed by a course of twelve injections of bismuth at weekly intervals, a second period of rest and

another twelve week course of bismuth. In patients with syphilis of many years' duration we may not use the rest and additional bismuth courses. However, we are inclined to use these additional bismuth courses if the patient remains 'Wassermann fast' or has syphilis of comparatively few years' duration. In our clinic in late latent syphilis we use the treatment scheme shown in Table XVIII.

TABLE XVIII  
SCHEDULE FOR TREATMENT OF LATE LATENT SYPHILIS<sup>1</sup>

<i>Time</i>	<i>Drug</i>
For 3-4 weeks	Bismuth in oil, weekly
8 weeks	Neoarsphenamine or arsenoxide, weekly
8 weeks	Bismuth in oil, weekly
8 weeks	Neoarsphenamine or arsenoxide, weekly
10-12 weeks	Bismuth in oil, weekly
8 weeks	Neoarsphenamine or arsenoxide, weekly
12 weeks	Bismuth in oil, weekly
Total 57-60 weeks	Totals Neoarsphenamine 24, Bismuth 33-36
<i>Additional Treatment</i>	
For 12 weeks	Rest
12 weeks	Bismuth in oil, weekly
12 weeks	Rest
12 weeks	Bismuth in oil, weekly
Total 48 weeks	Total Bismuth 24

<sup>1</sup> For dosage see Chapter v

Though an iodide may be indicated only during the first two or three months of treatment, if the patient becomes irregular in or lapses treatment, this drug may well be used again. Iodides probably should be used also with the bismuth courses following rest periods.

We do not feel rigidly bound by the above treatment schedule. In a relatively young syphilitic patient with an infection of five to seven years' duration, for example, we are inclined to treat the patient more like an acute case with four courses of arsenicals and intervening bismuth. On the other hand, in long standing infection, older age, and general debility we may treat the patient with heavy metal and potassium iodide only. Such a patient may be given six months of bismuth or bismuth courses alternating with mercury inunctions. At the end of this time he may be placed on a regime of alternating eight to twelve-week rest periods and twelve week bismuth courses until he has had three bismuth courses in addition to his original six months of heavy metal.

## PROGNOSIS

## EARLY LATENT SYPHILIS

Early latent syphilis, if no previous treatment has been given, but rarely gives rise to infectious relapse. A brief summary of what information is available regarding the effect of treatment on early latent syphilis follows. The Co-operative Clinical Group material indicates that of five hundred and fourteen treated early latent cases, one half showed satisfactory results, about one-third had unsatisfactory results, the remainder being still under treatment at the time of reporting. Unsatisfactory results included clinical and serologic relapse, "Wassermann fastness," and deaths. It is pointed out by Moore that the unsatisfactory results were mainly in the serologic field, since only 4 per cent of the early latent cases had subsequently developed clinical symptoms, and half of these were instances of infectious relapse. Therefore it would appear that possibly only about 2 per cent or so of treated early latent cases would subsequently develop late clinical syphilis. Measured by the Co-operative Clinical Group criteria of satisfactory results, Padgett, in a study of five hundred and fifty-one early cases of syphilis treated at the Johns Hopkins Hospital clinic, found such results in 58.7 per cent of forty-six cases of early latent syphilis. Seroresistance was the most common factor (in 32.6 per cent) in the cases with unsatisfactory results. This group of cases had been followed from five to ten years.

## LATE LATENT SYPHILIS

In late latency, as was pointed out earlier in this chapter, the only clue with regard to what may be expected without treatment is that offered by Bruusgaard. Moore has published some estimates of the outlook in latent untreated syphilis based on Bruusgaard's figures and his own. He indicates that the patient with late latent syphilis has only two or three chances out of ten of developing serious trouble as the result of his infection. (The term latent syphilis implies a negative spinal fluid, and therefore the danger of central-nervous-system involvement is past—beyond four years.)

The effect of treatment is difficult to evaluate in cases of serologic fastness. Again I must quote from the material of the Co-operative Clinical Group, a study of treatment results in 1,197 patients in the stage of late latency. Satisfactory results were obtained in one-third and unsatisfactory results in one-half, the remainder of the patients being still under treatment. Unsatisfactory results consisted of clinical and serologic relapse, "Wassermann fastness," and death.

Moore points out that only 4.8 per cent of the late latent group developed clinical relapse. After commenting upon the progressive decrease of

"Wassermann fastness" with the passage of years, and on the basis of his estimated probable outcome in untreated latent syphilis, Moore draws the following conclusions as to the results achieved by treatment in the stage of late latency. Assuming that the trend of the Co-operative Clinical Group's material is maintained, it would seem that satisfactory outcome is increased by treatment from 35 to 85 per cent. The percentage of latent cases with positive blood tests is reduced from 35 to 7.5 by treatment, and the chance of the development of late lesions of syphilis is reduced from 20 to 30 per cent to 2 to 5 per cent.

The reader must remember that some of these figures are estimates, and that others probably were influenced by factors which make accuracy impossible. However, the fact remains that the figures of the Co-operative Clinical Group are the only ones of such extent available to give us any idea as to the effect of antisyphilitic treatment on the prognosis in latent syphilis. From the Co-operative Clinical Group's material, Moore points out that in the 4.8 per cent of late latent cases that presented clinical relapse, the majority had had less than twenty injections of an arsenical. One-third each of this group developed cardiovascular syphilis, central-nervous-system syphilis (no cases of tabes or paresis), and late benign lesions.

Serologic fastness in latent syphilis is a problem which causes the practitioner a great deal of worry. In our contact with general practitioners and health officers in postgraduate work, we find that this causes them more concern than any other problem in the management of syphilis. This is true for various reasons. First, it is encountered more frequently than other troublesome problems since latent cases make up the bulk of the syphilitic patients. Secondly, if the physician lacks the proper conception of the meaning of serologic fastness he will feel that it means persistently active infection in spite of treatment. (He can substantiate this belief by the writings of some syphilologists and serologists.) Thirdly, in this day of constant "blood-testing" of the public at large, in industry, in food handlers, in schools, for premarital examinations, and under many other circumstances, a persistently positive blood test for syphilis proves embarrassing to the patient. He therefore insists that his physician do something about it.

The fundamental factors concerned with serorelapse and serologic fastness have been discussed in Chapter IV, and the reasons for this state in early syphilis have been covered in Chapters VII and VIII. "Wassermann fastness" is that condition in which the positive blood test does not reverse under treatment within the expected period of time. The drop in the titer of reagin in the blood under treatment is not so precipitous in latent syphilis as in acute syphilis. The gradual decline in titer accounts for the fact that a serologic reversal in late latency is not expected until almost a year or so

after treatment was begun. Therefore it is not surprising that a relatively high percentage of late latent cases do not show seroreversal under treatment, in the Co-operative Clinical Group, 35 per cent maintained serologic fastness in spite of all forms of treatment. In addition to the above comment, it should be noted that in the presence of tertiary syphilis in bones, liver, the cardiovascular system, and of the central nervous system, serologic fastness occurs in a high percentage of instances. Thus with "Wassermann fastness" in the case of apparently late latent syphilis, the attending physician must be sure that one of these late lesions is not present.

As an answer to the question of the significance of, or prognosis of latent syphilis associated with "Wassermann fastness," I can do no better than to quote Table XIX, from the Co-operative Clinical Group's statistics. It indicates that "Wassermann fastness" does not indicate a poorer prognosis

TABLE XIX

COMPARISON OF THE INCIDENCE OF RELAPSE IN LATENT SYPHILIS IN PATIENTS WASSERMAN FAST<sup>1</sup> VERSUS PATIENTS WHOSE WASSERMANN'S REVERSE DURING TREATMENT<sup>1</sup>

	<i>Percentage Incidence of Relapse</i>						
	<i>Total Patients</i>	<i>All Types</i>	<i>Early Infectious</i>	<i>Benign Late</i>	<i>Central Nervous System</i>	<i>Cardiovascular</i>	<i>Visceral</i>
Wassermann fast	526	4.6	0.2	1.1	1.1	1.9	0.4
Wassermann not fast	1185	5.7	1.3	0.6	2.1	1.7	0.2

<sup>1</sup> From Ven. Dis. Inform.

With the passage of time, the tendency to spontaneous reversal of the serologic tests becomes manifest. This is encountered by anyone following the subsequent course of treated syphilitic patients. The Co-operative Clinical Group's material showed "Wassermann fastness" to decrease with the duration of the observation period after treatment was stopped, as follows: at less than two years, 51 per cent were "Wassermann fast", two to five years, 31.6 per cent, five to ten years, 20.9 per cent, and more than ten years, 7.5 per cent. This tendency to spontaneous reversal with the passage of the years, in my opinion, contains the answer to those who maintain that treatment continued for years may eventually lead to seroreversal in the serologic fast case.

The answer to the practitioner's question as to what "Wassermann fastness" means in prognosis can be answered in the following manner. The available evidence to-day indicates that a certain fairly high percentage of serologic fastness is to be expected in the patient treated for late latent

*syphilis* Irrespective of this, the patient runs no greater risk of late clinical syphilis than does the one in whom reversal has taken place under treatment. Furthermore, nothing can be done to reverse the blood, and time eventually will do so in most instances.

## INSTRUCTIONS TO THE PATIENT

The patient with latent syphilis should be informed of certain facts

In early latency, especially if he has by chance been inadequately treated, he must be informed that he is a potentially infectious individual, and he must understand the danger he offers, especially to his sexual partner. He should know that his sex contacts must be investigated for syphilis. Such a patient can, however, be assured that with adequate regular treatment, as outlined in the discussion on secondary syphilis, he will subsequently have slight chance of showing infectious relapse, and thus, after treatment, marriage will be possible.

The patient in the late latent stage, having had syphilis of more than five or six years, can be assured that his chance of being infectious to sexual partners or other contacts is nil. However, he as well as the patient in early latency must understand that he carries within him a dangerous infection that may lie smouldering for years or even decades, then to become manifest with deforming skin, bone, or mucous-membrane lesions, with disabling or fatal cardiovascular or central-nervous-system disease. Because he feels so well at the moment, it at times will take all the persuasive powers of the physician to convince the patient of these dangers and the need for over a year's treatment consisting of weekly injections. The need for periodic examinations subsequent to treatment must be understood.

Every female in the latent stage, either early or late, must be made to realize the risk of syphilitic infection in the fetus should she become pregnant. If she has had her infection and treatment before marriage, she must understand that treatment is essential during pregnancy. To avoid future misunderstandings, her husband should be aware of her infection and the need for antisyphilitic treatment in pregnancy.

Lastly, every patient with latent syphilis should know at the beginning of treatment that there is a certain likelihood that serologic reversal will *not* take place under therapy. But the patient also should realize that this is to be expected in a given percentage of cases, and that his physician knows the amount of treatment necessary in spite of serologic fastness. I have come to feel that this phase of the ultimate result must be presented early and honestly to forestall unpleasant consequences. Persistently positive serologic tests may cause the patient to wish for a change of physicians. More unfortunate, however, is the production of syphilophobia. If the patient has been led to believe that "cure" and serologic

reversal are synonymous, his life and morale may be shattered by the realization that his blood test will not become negative. Every one treating a considerable number of syphilitic patients has known the patient who goes from physician to physician begging reassurance and more treatment, subjecting himself to repeated spinal-fluid examinations and blood tests because of serologic fastness. Such a patient often has adopted the mental attitude that no one will treat him further because he is so "eaten up inside," as one patient expressed it, and thus is in a hopeless condition. Suicide is at times the result. All this can be avoided by the proper interpretation of "Wassermann fastness" and prognosis before treatment is begun rather than at the end of treatment, when such an explanation often appears as a lame excuse for a poor result.

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## X

### LATE BENIGN SYPHILIS

#### HISTORICAL NOTE

SOME of the late lesions of syphilis were recognized in the early part of the sixteenth century. In 1514 De Vigo called attention to the nocturnal pains of syphilis of bone, as well as to the occurrence of certain *gummatous manifestations*, *iritis*, and *nasal ulceration*. ("Classic Descriptions of Disease," Major.) The seventeenth century provided descriptions of visceral syphilis, while Wilks and Virchow made valuable contributions to the knowledge of this phase of syphilis in the nineteenth century.

#### COURSE OF INFECTION

After the generalized invasion of the body by the *T. pallidum*, early in the course of syphilis, the disease may follow one of two courses. The infection may become quiescent (latent) at once, or may express itself by the reaction characterized as the secondary stage, subsequent to which latency becomes established.

As was shown in Chapter II, the subsequent progress of the disease may follow one of two courses, or both, from the pathologic viewpoint. Though organisms are few in the syphilitic foci, they may call forth reactions which may be profound. As a result of the host's immunity, the reaction to these few organisms may be either proliferative or destructive. In latency this tissue reaction may be so mild that, unless vital tissues are involved, the patient may remain in the clinically latent state during the remainder of his life. As was indicated in the discussion of latency, the outlook of at least one-half of all untreated syphilitic patients is just that.

#### PROLIFERATIVE REACTIONS

However, in certain individuals, unfortunately, the course of the infection is not so benign. The tissue reaction in some is essentially of a proliferative nature. Miliary gummata occur frequently, being replaced by a rapidly fibrosing process before tissue destruction develops to any degree. The truly proliferative reaction is first an inflammation characterized by perivascular infiltration with lymphocytes and plasma cells. This is followed by the appearance of fibroblasts and subsequent fibrosis. Such a reaction may continue for a long time until much of the structure of certain organs has been involved. Eventually, as is so beautifully demonstrated in the cardiovascular and central nervous systems, such a proliferative scarring process reaches the point where the functions of the part are impaired, with resulting clinical manifestations. It must be recognized



that even in a predominantly proliferative process a destructive element may play a part

### DESTRUCTIVE REACTIONS

Destructive reactions in late syphilis are presumably associated with a different type of immune response. The gummatous reaction is looked upon as an 'allergic' phenomenon. Apparently in certain instances, the tissues of the host become sensitized to the parasite, or its products. Subsequent activity of the organism at such a sensitive site produces a violent, explosive reaction, the gumma. This type of reaction is likely to occur in the skin, mucous membranes, bones, and viscera. Characteristically tumour formation, varying from microscopic size to more than 5 cm in diameter, takes place. The gummatous granuloma shows a tendency to undergo necrosis at its centre, with resultant tissue destruction. This gummatous reaction is the fundamental lesion producing the clinical picture of late benign syphilis.

**Pathology** The remarkable thing about the gumma is the extensive reaction which is caused by the presence of so few organisms. The *T pallidum* is present in such small numbers that its presence may be demonstrable only by animal inoculation experiments. Treponemata are to be found neither by the darkfield examination nor by microscopic examination of the tissue. Microscopically, the small gummata are found to consist of masses of epithelioid and round cells. With the growth of these masses and an accompanying vascular occlusion, necrosis will occur. In the early stages of the gumma giant cells may be present. As the gumma enlarges granulation or fibrous tissue will be found at its borders. This represents an attempt at repair on the part of the surrounding tissues. At times several gummata may coalesce. Grossly, on section, gummata present a grayish white colour, with a granular or caseous centre and a translucent border of dense fibrous tissue. Because of their destructive nature, gummata heal with resulting dense and deforming scars. The gumma may be a hard tumour until its centre has undergone necrosis, whereupon it presents a sense of elasticity when palpated.

From a pathologic as well as a clinical viewpoint (as may be noted in some of the subsequent case reports), it should be recognized that the patient reacting with a gummatous type of lesion has had this inherent tendency, possibly for years (Case 56). Therefore a search will often reveal the scars of such a previous granulomatous process.

### INCIDENCE

The late benign manifestations of syphilis occur commonly in from three to ten years after infection is acquired. However, this time relation

ship should not be too rigidly accepted. Precocious tertiaryism may occur at the end of the secondary stage. Again, the first benign tertiary lesion, in so far as one can determine by clinical examination or by history, may occur as late as thirty five to forty years after infection. Such a lesion was seen in our clinic within the past year in a white man who gave an excellent history of acute syphilis in 1905. As far as he knew and we could determine, the cutaneous syphilitid which brought him to the clinic was the first manifestation of his disease since the acute stage.

It is said that late benign syphilis is becoming less frequent. This is probably true for two reasons. In the first place, the greater the number of syphilitic patients treated in the early and latent stages, the more infrequently will the late lesions be seen. Secondly, with a better grade of medical practice generally, and a public more health minded, fewer examples of neglected skin or mucous membrane ulcerations, with their subsequent disfiguring scars, will be encountered.

#### FREQUENCY AND DISTRIBUTION

Among 6,259 cases of syphilis which have been admitted to the Vanderbilt University Hospital Syphilis Clinic since 1925, there have been five hundred and sixty-one instances of late benign syphilis, an incidence of 9 per cent. Some of the cases presented more than one tertiary manifestation. In Table XX the late benign lesions have been classified as to the structures involved, as well as to race. Neither race seems to be especially

TABLE XX  
DISTRIBUTION OF LATE BENIGN LESIONS AS TO SITE AND RACE

<i>Site</i>	<i>Negro</i>	<i>White</i>
Skeletal (all types)	122	39
Skin	121	43
Upper respiratory tract (nose, throat, larynx)	49	18
Mucous membrane (mouth)	41	15
Eye (all types)	43	11
Visceral (liver, stomach, etc.)	18	9
Lower respiratory tract (?)	2	2
Mediastinum (?)	3	1
Lymph nodes	7	—
Genital tract (female)	4	—
Penis	3	2
Testis	3	1
Skeletal muscle	3	1
Totals	419	142

predisposed to these lesions. Negroes made up 67 per cent of all admissions to the Syphilis Clinic, and 74 per cent of the late benign lesions of syphilis occurred in the coloured race. These figures do not represent the actual frequency since patients with certain tertiary lesions are more likely to be admitted to the hospital than to the clinic, and subsequently be returned to treatment agencies elsewhere. For example, more cases with gumma of the liver will be admitted directly to the hospital by the admitting officer, than, let us say, cases of tertiary syphilids of the skin. However, the following table will provide an index of the relative frequency and distribution of late benign syphilitic lesions in the various tissues of the body, as encountered in our Syphilis Clinic.

As may be seen from the above table, no tissue of the body is immune to gummatous involvement. *The importance of this fact cannot be over emphasized.* Syphilis, perforce, must enter into consideration in the diagnosis of any ulcer, tumour, or granuloma occurring in the human being. The late manifestations of this disease must therefore be of interest to every specialist, irrespective of his field, and of especial interest to the general practitioner since he is the key man most likely to see the greatest number of tertiary lesions. His familiarity with the characteristics of tertiary syphilis will keep many a patient in his hands, eliminating the necessity of consultation with a specialist.

No one appreciates better than does the author the infrequency with which the benign tertiary lesions of syphilis occur in the clientele of the private practitioner. Because of this infrequency the possible syphilitic etiology of a given ulcer or tumour may not be considered. It is unfortunate that the index of suspicion is so low with regard to syphilis under these circumstances, for the diagnosis can be so readily established. Probably only in the secondary stage of syphilis is the serologic test for syphilis more frequently positive. In other words, seronegativity in late benign syphilis is very uncommon. The syphilitic basis for a lesion in question, in the presence of a positive blood test, can be readily confirmed within a few weeks by the institution of antisypilitic treatment.

Occasionally, in this phase of syphilis, in the presence of a negative blood test, the therapeutic tests of antisypilitic treatment may be indicated. Unlike the rules laid down in the diagnosis of acute syphilis, a positive laboratory report may not be essential to confirm a clinical impression. In acute syphilis, antisypilitic treatment before confirmation by laboratory procedures may wipe out the later confirmation of the diagnosis by the laboratory examination. Physician and patient are then committed to approximately seventy weeks of treatment with the attendant problem of safety in a prospective marriage and the like. The therapeutic trial of antisypilitic treatment in a seronegative patient presenting an ulcer, tumour,

or granuloma which may be a tertiary lesion is justified by expected prompt results in the resolution of the lesion. If no response occurs, treatment may be stopped. In connection with this discussion, I wish to emphasize what every clinician should know, that all lesions which might suggest syphilis in a seropositive case are not necessarily of syphilitic etiology. *The patient in syphilitic latency may suffer from other diseases.* The recognition of this fact is essential in cases in which a neoplastic process may need to be considered in the diagnosis.

The following sections of this chapter will be given over to a presentation of the clinical pictures of tertiary involvement of the various structures of the body. Some sections necessarily will be very brief because of the rarity of involvement of certain viscera. Yet their inclusion in this volume is justified for the sake of completeness. It will be quite obvious to the reader that the discussion of the differential diagnosis of rare tertiary lesions must be curtailed. For example, there is no excuse for the detailed discussion of the differential diagnosis of gastric syphilis from carcinoma or peptic ulcer of the stomach. In the discussion of the rarer forms of late syphilis it is my plan merely to indicate the conditions which must be considered in the differential diagnosis. The reader, if he finds it necessary, may then consult the appropriate textbook on medicine, surgery, otolaryngology, and the like.

## SYPHILIS OF THE SKIN

There are several good reasons for considering first the tertiary lesions of the skin. They are one of the most frequent of the late benign lesions. *Certainly, they are most frequently diagnosed because of the ease with which they may be examined.*

Secondly, tertiary skin lesions are very prone to leave landmarks which are quite characteristic and often diagnostic. The presence of such sign posts, if recognized for what they are, may be of importance in the recognition of syphilis as the etiologic factor in some later disorder.

Thirdly, the gummatous skin lesion, being visible, permits us to visualize by analogy the progress of the gumma which is deep-seated—in the viscera, for example. We can imagine the tumour formation, the necrosis which occurs in its centre, and depending upon its site, the development of an ulcer. Furthermore, after having observed the healing of the cutaneous gumma, we can visualize the resolution of the visceral gumma under treatment, and the subsequent scarring.

## CLASSIFICATION OF LATE SYPHILIDS

Dermatologic nomenclature includes three terms descriptive of the late cutaneous manifestations of syphilis. These are (1) nodular (tubercular),

(2) nodulo-ulcerative, and (3) gummatous. The fundamental pathology is the same in all of these, the clinical picture varies with the degree of the process, and the site. At one extreme is the nodular lesion in which the process consists of small gummata without sufficient breakdown of tissue to lead to ulceration, but with replacement by fibrous tissue leading to scarring. At the other extreme, the solitary gumma involving the subcutaneous tissues is characterized by necrosis and ulceration.

#### GENERAL CHARACTERISTICS

A knowledge of certain features of tertiary syphilids will lead to suspicion that a given skin lesion is syphilitic, and will differentiate it from the manifestations of the secondary stage.

The fundamental lesion is a papule, characterized by deep induration and a low-grade inflammatory reaction. In contrast to secondary syphilis the tertiary syphilids at most are few in number and often are solitary. The lesions tend to be asymmetrically disposed. At times they are painful. Nodules tend to be so grouped that they form patterns of segments of circles. Healing and extension of such serpiginous lesions are common. The broken-down syphilids typically present indolent "punched-out" ulcers. Healing of both nonulcerative and ulcerative lesions generally leaves a noncontractile, atrophic scar, the borders of which may show a long standing hyperpigmentation.

As has been indicated elsewhere there is a paucity of organisms in the lesions so that darkfield examination of material from late syphilids is negative. Thus these lesions may be considered noninfectious. The serologic tests for syphilis are positive in over 90 per cent of cases of tertiary syphilids.

**Nodular and Nodulo-ulcerative Lesions.** As has been indicated, the basic lesion in this type is the deeply seated indurated papule. It is brownish red in colour, and varies in size from a pinhead to a pea. Such lesions have a predilection for the face, scapular and interscapular regions, and the extremities. The papules may remain unchanged for weeks or months. Resolution may occur without breaking down. If they do break down to form superficial ulcers the lesion is described as nodulo-ulcerative. In either event involution is followed by a thin, atrophic, noncontractile scar, except in some cases treated early. These scars, consisting of individual ones arranged in arciform patterns, act as important landmarks of syphilitic infection (Case 56).

**Case 56.** A white female, aged nineteen years, was first seen in 1932 because of pain in the right leg for two months and pain in the eyes for three weeks. There was no history of acute syphilis. The ophthalmologist made a diagnosis of interstitial keratitis. Roentgenograms showed osteitis and periostitis of the right

tibia and fibula. An ulcer was present on the left forearm. Blood Wassermann and Kahn tests were positive. The patient received arsphenamine 0.3 Gm.  $\times$  11, and bismuth  $\times$  22, after which she was still seropositive. Treatment was lapsed.

The patient was next seen in 1939 because of an ulcer of the leg. Examination at this time showed atrophic annular scars on both forearms and both legs. A "punched-out" ulcer about 1 cm. in diameter was present on the upper third



FIG 45 Scars of nodulo-ulcerative syphilid (Case 56)

of the left leg. Blood Wassermann and Kahn tests were negative on more than one occasion. The ulcer of the leg healed promptly under antisyphilitic treatment.

**Comment.** Figure 45 shows typical scars, landmarks of previous tertiary skin lesions. The scars are atrophic and depressed, with a characteristic annular pattern. Lateral to the depressed semicircular scar on the patient's right arm there are, by contrast, several scars due to burns. This patient on her second admission presented the unusual finding of consistently negative blood tests for syphilis in the presence of a late benign lesion which responded promptly to antisyphilitic treatment (Fig 45).

In most instances the lesions present a superficial, progressive process. Nodules disappear usually with some scarring, and new ones appear at the margin of the previous site. Thus there is a progressive, ever-widening



FIG 46 Tertiary syphilis—nodular syphilid (Case 57)

serpiginous or arciform lesion. This process may go on for years so that wide areas, such as the whole back, for example, may have been covered by the progressing lesion. As the syphilid enlarges the nodules may be so scattered that the observer loses sight of the pattern of segments of circles. This must be remembered as typical of the nodular or nodulo ulcerative type. Cases 57, 58, and 59 are of this type.

**Case 57** A twenty three year-old white married man had had a penile lesion eight years before, for which he received thirty-eight intravenous and thirty

eight intramuscular injections somewhat irregularly. He married one year after having had the penile lesion. Two years later his wife gave birth to a stillborn child. The patient had been seen in the Surgery Clinic of the Vanderbilt University Hospital four and seven years after the penile lesion. Each time the Kahn test was negative. About five months before being admitted to the Syphilis Clinic the patient developed "ringworm." He had had headache for one week.

Fig 47

Fig 48



FIG 47 Tertiary syphilis—nodular syphilid (Case 58)

FIG 48 Tertiary syphilis—nodular syphilid on pubes solitary gumma of penis (Case 58)

Examination disclosed red annular lesions on both wrists. The borders were elevated, the centres atrophic and depressed. Over the forearms were scattered numerous smooth papules arranged in annular patterns. Some of the papules were covered with scales. On the left knee, anteriorly and in the popliteal space were found involuting annular lesions with pigmentation and atrophic scarring. Blood tests were reported as follows: February 14, Wassermann positive, Kahn negative; February 22, Wassermann and Kahn both positive; March 29, Wassermann positive and Kahn negative. Spinal fluid showed globulin positive, cells 2 per cu mm, Wassermann test positive in all dilutions, and a flat mastic curve.

**Comment.** The lesions in this case were of the typical nodular type and occurred in a patient who had had much irregular treatment early in the course of syphilis. Asymptomatic neurosyphilis was also present. The fluctuating Kahn test may have accounted for the negative tests on previous visits to the hospital. Response to treatment was rapid (Fig 46).

**Case 58.** A thirty-five-year-old white male had a penile lesion nine years previously. It was present four weeks and disappeared after two intravenous



injections Two months before admission to the Medical Clinic the patient noted a "pimple" on the dorsum of the penis It gradually increased in size and became crusted Five weeks after the appearance of the first lesion, others appeared on the scrotum, penis, and knee

Examination revealed a crusted lesion, about the size of a sixpence, on the dorsum of the penis A similar smaller one was found at the base of the shaft on



FIG 49 Tertiary syphilis—nodulo ulcerative syphilid (Case 59)

the right side To the left on the pubes and on the inferior aspect of the penile shaft there were numerous papules arranged in an annular pattern Some were ulcerated and crusted A similar annular lesion several inches in diameter was present on the right knee-cap The patient also presented the signs of aortic insufficiency Blood Wassermann and Kahn tests were positive

**Comment.** The first solitary penile lesion might have raised the question of a chancre Its ulcerative, crusted character and previous history would make this diagnosis improbable The presence of the nodulo-ulcerative syphilids elsewhere and the aortic regurgitation made the diagnosis of tertiary syphilis The lesions involuted following the administration of iodides and two injections of bismuth Subsequent recurrence took place after a lapse of treatment (Figs 47 and 48)

**Case 59** A sixty six year-old Negro was admitted to the Syphilis Clinic because of pain in the right leg Drainage from the upper part of the right leg had been present off and on for twenty years Blood tests for syphilis had been positive one year before admission to the clinic The history was unreliable

Examination revealed multiple skin lesions involving all extremities, and the trunk, front and back The syphilids appeared as individual nodules, some of

which had broken down and presented ulcers exuding purulent material. Others were covered with crusts. In general the nodules were arranged in a pattern which had polycyclic borders. On the forehead were several isolated nodules in the skin. There were many atrophic scars scattered over the body. These presented serpiginous borders. The legs, especially the right one, revealed extensive ulceration and scarring of a long standing process. The right tibia



FIG 50 Tertiary syphilis—nodulo-ulcerative syphilid draining sinus from osteitis (Case 59)

was found to be thickened on palpation. In its upper end was a cavity several centimeters deep, with an opening through the skin 3 cm in diameter. Foul, purulent drainage exuded from this cavity. Roentgenogram of the tibia showed marked thickening of the periosteum and two large areas of bone destruction, one in the middle and one in the upper third. Blood Wassermann and Kahn tests were positive.

**Comment** This patient's history was obviously of no value. From the number of scars found upon the body, it was apparent that recurrent syphilids had appeared for many years. The bone lesion was of long duration. After two injections of bismuth in oil and the use of potassium iodide, all nodules had flattened out, all ulcers had healed, and all crusts had disappeared. Scars remained as residuae. The cavity in the bone gradually closed in. At the end of five months of treatment, when the patient was last seen, roentgenologic study showed much improvement, though there was still an excavation in the bone with a draining sinus (Figs 49 and 50).

**SQUAMOUS OR PSORIASIFORM SYPHILID** A variation of the nodular type is the so-called squamous or psoriasiform syphilid. This lesion consists of a plaque of grouped papules covered with a waxy scale. Such syphilids are especially found upon the palms and soles, where there is little tendency to ulceration or scarring (Case 60).

**Case 60** A forty four year-old white male, twenty five years before had a penile lesion which lasted for ten days. About eighteen months before, the palm of his hand cracked open. His physician found his blood to be positive for syphilis, and he received only bismuth for one year. Healing was quite prompt. He had had no treatment for four months before admission to the Syphilis Clinic. The palmar lesion had recurred one month before admission.

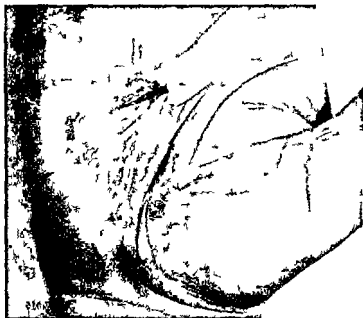


FIG 51 Tertiary syphilis—squamous syphilid (Case 60)

Examination showed on the palm an area about the size of a half-crown which was covered with shiny scales. In the centre was a deep fissure. Wassermann and Kahn tests were positive.

**Comment** This is a characteristic type of tertiary skin lesion. Healing was prompt upon the use of iodides and bismuth (Fig 51).

**Gumma of the skin** is a less frequent manifestation than the nodular or nodulo-ulcerative syphilid. It consists usually of a solitary lesion, or at least appears alone in a given area. In occasional cases gummata may be found simultaneously at several sites. This process is basically a subcutaneous lesion involving the epidermis secondarily. Gummata are found most often on the thighs, buttocks, legs, shoulders, forehead, and scalp. Trauma seems to play a part at times in the development of these lesions. I believe this to be especially true in the examples of precocious cutaneous gumma seen in early syphilis. Under such circumstances traumatized tissue apparently may present a tertiary type of reaction.

The cutaneous gumma is a circumscribed oval or round tumour varying in size from a pea to a walnut or larger, and may be painful. It may involve only the epidermis and corium, but commonly the subcutaneous tissue also is included in the process. The overlying skin becomes red, and then bluish-red or purple. There is no increased local heat. The tumour has a rubbery feeling upon palpation. Absorption may occur but more often

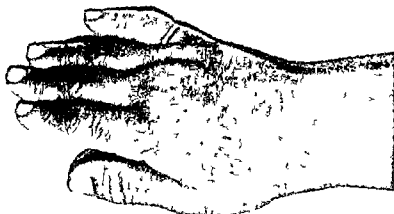


FIG 52 Tertiary syphilis—gumma of skin (Case 61)

necrosis takes place with the formation of an ulcer. Such ulcers have reddish or purple-coloured soft, necrotic borders. Typically they have a "punched-out" appearance. (See Cases 61, 62, and 63.) At times layered crusts cover the ulcers, so-called rupial gumma. In those instances in which underlying bone and cartilage are involved, the question arises as to whether the lesions actually began in the subcutaneous tissues or in the periosteum or perichondrium (Case 70). The scars of gummatous ulcerations may be extensive and disfiguring.

**Case 61.** A forty-two-year-old Negress was admitted to the Medical Clinic for complaints unrelated to the skin. About twenty-five years before, her first husband had genital lesions, and she also developed some at that time. Ten years later she had another genital lesion for which she received eight intravenous injections. Her blood test was positive one year before admission. She had noted a skin lesion only a few weeks before coming to the clinic.

Examination disclosed a skin lesion 2.5 by 3.5 inches in diameter on the dorsum of the right hand and wrist. The border was elevated and red in colour. Within the borders were several areas of slight depigmentation. Blood Wassermann and Kahn tests were positive.

**Comment.** This annular lesion healed promptly with but little depigmentation and no scarring. The lesion had been of such short duration that such residua did not occur. (Fig 52)

**Case 62.** A forty-one-year-old Negro complained of a sore on the chin. Six weeks before, while shaving, he cut a "lump" which was present under his chin. This failed to heal, increased in size, and was usually covered by a crust. He had had a penile lesion eight years before, at which time his blood was found "bad" and he was given six intravenous and two intramuscular injections.

Examination revealed a granulomatous ulcer of about the size of a crown

FIG. 53

FIG. 54

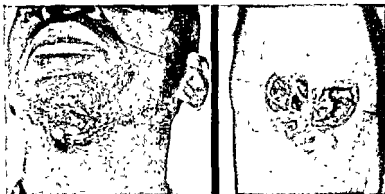


FIG. 53. Tertiary syphilis—gumma of skin (Case 62).

FIG. 54. Tertiary syphilis—gumma of skin (Case 63).

piece, involving the inferior aspect of the chin. It was tender, the edges were indurated, and some areas in the base of the ulcer were deeper and appeared "punched out." Blood Wassermann and Kahn tests were positive.

**Comment.** This represented a solitary gumma of the skin. The lesion was completely healed after bismuth  $\times 4$ , iodides by mouth, and neoarsphenamine 0.6 Gm.  $\times 1$  (Fig. 53).

**Case 63.** A thirty-four-year-old white housewife was admitted to the Medical Ward because of "sores." A year before admission, a "pimple" appeared on the inner aspect of the left thigh in its upper third. This gradually enlarged to become a large sore. About seven months before admission similar ones appeared on the right leg and on the tips of both shoulders. All persisted and gradually enlarged. The lesions all appeared as tender, painful, hard swellings which broke down to form ulcers in about four to five weeks. Though many physicians had been consulted, the ulcers were refractory to various types of local medication. Only one physician drew blood for testing, and received a negative report. The patient had been confined to her bed in the five weeks preceding admission to the hospital. There was no history of acute syphilis. She had been married thirteen years, and had had three pregnancies, all resulting in living, apparently healthy children.

Examination showed that the patient was poorly nourished. Five large ulcers were found upon the body. They varied from 4-8 cm. in diameter. The edges were undermined, and foul-smelling material exuded from them. The right

thigh presented an atrophic scar 5 by 7 cm in diameter. The photograph shows the partial healing with atrophic scar which occurred at the upper border of the ulcer of the left thigh. Blood Wassermann and Kahn tests were positive.

**Comment.** The ulcers represented ulceration of gummata of the skin. All lesions were completely healed after two months of antisyphilitic treatment. Noteworthy is the fact that a number of physicians had attended this patient, and that only one suspected syphilis, which diagnosis he discarded upon the receipt of one negative blood test (Fig. 54).

**Pseudochancere redux** is the term applied to the occurrence of a solitary gumma at the site of the original chancre which occurred years before. Obviously, this lesion is found most often upon the genitalia, and in the absence of proper evaluation may be thought to represent acute syphilis and reinfection.

#### DIFFERENTIAL DIAGNOSIS

A number of conditions must be considered in the differential diagnosis of tertiary syphilids. Some of these are common, varying from benign to serious skin diseases. Others are rare. The diagnosis of the cutaneous manifestations of tertiary syphilis on the basis of morphology requires the skill of the well-trained dermatologist. Therefore several hints are worthy of consideration by the average physician. If the observer will remember the characteristics of the lesions as described, make note of the distribution of the nodules and their tendency to the formation of thin, atrophic white scars, and if he has syphilis constantly in mind, relatively little difficulty will be encountered in the average case. Syphilis having occurred to the physician, he can fortunately obtain confirmation of his impression in over 90 per cent of cases by a positive blood test.

However, even if the serologic test seems to confirm the impression of syphilis, it must be recalled that nonsyphilitic lesions occur in syphilitic patients. Therefore, the final confirmation of the impression of syphilitic must be obtained by the effect of antisyphilitic treatment. Stokes warns that this is not always a safe criterion. Though this rarely may be true for practical purposes I believe the therapeutic effect is of value. If, after, the introduction of antisyphilitic treatment, no involution of the lesion has begun within two or three weeks, it will behoove the attending physician to look for an etiology other than syphilis, or to obtain consultation with a competent dermatologist.

In the nodular or nodulo-ulcerative type of syphilid, the granulomas, tuberculosis, leprosy, and the several mycotic infections must be considered in diagnosis. Actually, however, this type of late syphilitic lesion need be differentiated from only three common skin diseases, namely, psoriasis, seborrheic dermatitis, and epidermophytosis (ringworm). Psoria-

sis has a predilection for the extensor surfaces, never ulcerates, and is unassociated with scarring. Scraping off of the usually abundant scales reveals the typical bleeding points of psoriatic lesions. A history of long-standing recurrent lesions is common in this condition. Seborrheic dermatitis is usually limited to the scalp, face, sternal and interscapular regions. The skin is red, not indurated, and greasy scales cover the lesions. Ulceration and scarring do not occur. Ringworm or epidermophytosis is often confused with the nodular tertiary syphilid because of the arciform pattern. This is especially true on the palms or soles. In fungus infection the lesion is superficial, and at the borders may be seen pinpoint-sized vesicles or pustules. Scrapings from these, if macerated in sodium hydroxide and examined with the microscope, may show the etiologic organisms. Epithelioma must, at times, be differentiated from the nodulo ulcerated syphilid. The borders of the cancer are usually indurated. Worthy of note is the fact that epithelioma may develop in a long standing tertiary syphilid. Under such circumstances one may observe a rapid involution of the lesion under antisyphilitic treatment except for one area which seems to be resistant. Biopsy may reveal that the tissue is malignant (Case 64).

**Case 64** A fifty four year-old white man complained of "ringworm" on the chest of eight years' duration. This was described as consisting of nodules. Two years before admission he was found to have 'bad blood' and was given intravenous and intramuscular injections, ten of each. The 'ringworm' began to ulcerate and to be covered with crusts six months before admission. He received a few more injections, the last having been given shortly before admission.

Examination disclosed, at the second interspace to the right of the sternum, an area 2.5 by 1 in. in diameter, most of which consisted of healed, reddish, pigmented skin surrounded by a halo of pigmentation. At one border was an area of ulceration, with a raised edge, the size of a shilling. Roentgenogram showed no involvement of the ribs. Blood Wassermann and Kahn tests were positive.

The patient received arsphenamine 0.4 Gm  $\times$  8, and bismuth  $\times$  8. The ulcer decreased in size to that of a threepence. This would not heal. Biopsy revealed a basal-cell carcinoma.

**Comment** The 'ringworm' of eight years' duration was no doubt a nodular tertiary skin lesion. The ulceration of six months' duration healed under treatment received elsewhere and in our clinic, except for the resistant area shown to be malignant.

The single gummatous cutaneous lesions, in their early nonulcerated stage, may simulate benign or malignant tumours and sebaceous cysts (especially of the scalp). As they break down they may suggest furuncles.

and carbuncles except for their "cold" character. As in the nodular type, certain mycotic infections may be simulated. Stasis ulcer of the legs must be differentiated from gummatous syphilis (Case 59). This may be difficult at times. The presence of varicose veins, edema, brawny induration, and a history of previous subcutaneous rupture of veins will be of aid in differentiation. The presence of ulcers of the legs in Negroes may raise the question of sickle-cell anaemia as against gumma.

In the past elephantiasis of the external genitalia in both sexes has usually been considered to represent a rare late benign syphilitic complication. With the growing knowledge of lymphopathia venereum, there is reason to believe that syphilis plays no part in this condition. The cases of syphilitic elephantiasis reported in the past have no doubt been due to lymphopathia venereum in patients with latent syphilis in those instances in which positive blood tests were obtained.

## SYPHILIS OF THE MOUTH, TONGUE, AND THROAT

Next to late benign syphilis of the skin, tertiary lesions of the mouth and pharynx are probably the most commonly recognized tertiary lesions. Most frequently they involve the soft palate, tonsillar fossae, posterior pharyngeal wall, and less commonly the tongue and lips. Gummatous disease of the hard palate is not rare, but it probably always begins as disease of the bone underlying the mucosa.

The nodular or nodulo-ulcerative lesions of the skin adjacent to the lips may extend to involve the lips themselves. Solitary gumma of the lip may present as a tumour which may or may not break down to produce ulceration. A diffuse infiltration of the lip has been described as occurring rarely. Some authors have questioned whether such lesions are always syphilitic. Gummatous ulceration may occur at the angles of the mouth.

From a pathologic viewpoint the tertiary mucosal lesions are like those of the skin. A localized syphilitic inflammation becomes established and characteristically goes on to tumour formation, necrosis and ulceration. This is followed by scarring with deformity, and often by perforation of structures such as the soft palate.

## CLINICAL PICTURE

The clinical picture is worth reviewing as an aid in the differentiation of this lesion from other diseases of the oropharynx. Commonly the complaint is that of "sore throat," but noteworthy is the story of chronicity—a story not of a duration of days as in common acute infections, but of weeks or even months. Analysis of the complaint reveals that the "sore throat" is not actually painful, but suggests rather a discomfort upon swallowing. In other words the physician gains the impression that the



primary difficulty is not one of pain, but rather a mechanical one due to the infiltration. A complaint of hoarseness, bad taste, and foul breath may accompany the story.

The results of examination vary with stage of the process. A description of the progress of a late lesion in the soft palate may be used as an illustration. In its nonulcerative stage, the gummatus infiltration will present a nontender thickening of a segment (say one-half) of the soft palate, or a tonsillar pillar, or tonsil, or uvula. Often the structures involved appear pale and almost edematous. At times they may present a violaceous colour. At this stage the process may involute without ulceration. Probably this does not occur often, though its frequency is difficult to determine since recognized cases usually are treated. (Such a lesion subsides promptly under antisyphilitic therapy.) Usually the process goes on to tumour formation. Under such circumstances, the soft palate, for example, may present a tumour the size of an almond or a cherry. Then, in the natural course of the disease, ulceration occurs.

The resulting ulcer is firm to palpation with the gloved finger, but not tender. It is covered with a dirty white exudate, and does not present the surrounding redness suggestive of acute infection. Ulcerated gummata are destructive lesions, and there may be widespread loss of tissue. Perforation of the soft palate or tonsillar pillars is common. Healing takes place with extensive scarring and anatomic deformity. As a result, regurgitation of food through perforations may occur, and a nasal tone to the voice may develop (Case 65). *Deformities and perforations of structures of the oropharynx encountered in routine examinations are valuable signposts pointing to syphilitic infection.*

**Case 65** A thirty-four-year-old Negress complained of "sore throat" of six months' duration. Hoarseness and dysphagia had been present three months. There was no history of acute syphilis.

Examination revealed a dirty white ulcer 2 cm. in diameter at the junction of the hard and soft palates. A perforation of 3 by 10 mm. was present in the centre of the ulcer. Palpation of the ulcer showed it to be infiltrated and firm. Blood Wassermann and Kahn tests were positive.

**Comment.** Under treatment with bismuth and iodides the mucosal lesion quickly healed. Due to the tissue destruction, residual deformity developed. The perforation in the palate has remained, though it causes only slight difficulty upon the swallowing of liquids. The soft palate now deviates to the right side and a deep indentation is present in the free edge between the uvula and the anterior faucial pillar (Fig. 55).

In the rare cases of tertiary lesions of the tongue the above course may be followed. Here a circumscribed tumour may develop, especially near

the midline and toward the middle or posterior part of the tongue (Case 66). This may break down to form an ulcer. If involution occurs either with or without ulceration, a deep cicatrix results though there may be exceptions in cases without ulceration. It is said that a diffuse gummatous infiltration may lead to chronic interstitial fibrosis, which produces a rough tongue and one without papillae.



FIG 55 Tertiary syphilis—gumma of soft palate (Case 65)

**Case 66** A fifty-three-year-old white widow complained of a swelling of the tongue of seven months' duration. It had gradually increased in size, and caused but little pain, mechanically the swelling interfered with swallowing to such an extent that her food intake was decreased and there had been a loss of 10 lb in weight. She had been given potassium iodide several days before being referred to the Syphilis Clinic, and the tumour had begun to subside. There was no definite history of acute syphilis. Some three months after the birth of her first child twenty six years before, she developed a very severe ulceration of her mouth. Her next two pregnancies ended in miscarriages. The patient's husband had died of "apoplexy" at the age of forty two years. She was known to have positive blood tests for syphilis ten years before admission to the clinic.

Examination showed that the tongue contained a large, circumscribed swelling which involved the posterior two-thirds of its right half. This tumefaction was slightly tender and firm, though not hard. Blood Wassermann and Kahn tests were positive.

**Comment** Involution of the tumour was complete after bismuth  $\times 3$ , and arsphenamine 0.3 Gm  $\times 2$ . In spite of somewhat irregular treatment in the following 2.5 years (arsphenamine 0.3 Gm  $\times 28$ , bismuth  $\times 42$ , and courses of iodides) she remained "Wassermann fast." Five years after the last treatment she was again seen because of carcinoma of the vulva. The blood was sero-negative at this time.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of late benign lesions of the oropharynx involves the consideration of only a few diseases. Usually, at the time the patient is seen the condition has been present too long for any serious consideration to be given to acute tonsillitis, peritonsillar abscess, and the like. The intense inflammatory reaction, systemic symptoms, fever, and regional lymphadenitis so characteristic of acute infections are all lacking. The same holds true with respect to Vincent's angina. Tuberculous ulcers, though chronic, tend to develop more rapidly, are more superficial, and practically always extremely painful in contrast to those of tertiary syphilis. Furthermore, tuberculous ulcers in the absence of advanced pulmonary tuberculosis are extremely rare. Carcinoma may be simulated, and this is especially true of gummatous ulcer of the tongue. However, the latter lacks the hardness, pain, and lymph-gland involvement which occurs in malignant disease.

Finally, it should be remembered that the blood tests for syphilis are usually positive, and furthermore, that response to antisyphilitic treatment will be prompt. If such response does not occur within two to three weeks of the institution of treatment, further study, biopsy, and the like is indicated.

Leukoplakia deserves merely a word. These white patches which develop on the mucosa of the mouth and tongue in the later years of life have in the past been thought to be related to syphilis. This viewpoint is being questioned at the present time. That malignant degeneration tends to occur in this lesion is common knowledge. Ulceration demands biopsy.

## SYPHILIS OF THE RESPIRATORY TRACT

The late benign lesions of the respiratory tract, except those of the larynx, are rare and will not be considered in detail. Lesions in the various structures of the tract probably originate as gummatous reactions in the wall of the air passages, or in some instances by extension of an extrinsic gummatous process to involve them.

## THE LARYNX

Late syphilitic disease of the larynx is not especially rare, as is indicated in Table XX. (See Case 67.) Pathologically it presents a gummatous infiltration of the laryngeal mucosa which, if ulceration takes place, may lead to rather extensive tissue destruction. In the event of widespread ulceration, sloughing of some of the laryngeal cartilages may occur with resulting deformity. (This type of syphilitic laryngitis is different from

that occurring in the secondary stage of syphilis. In the latter a more acute process associated with mucous patches may be present.)

The symptoms bringing the patient to the physician are usually hoarseness of varying degree, and at times stridor. Difficulty in swallowing may occur if the epiglottis has been involved in an ulcerative process. Examination with the laryngeal mirror may reveal tumefactions varying from pin-head to bean size in the mucosa above the vocal cords or at the base of the epiglottis. If necrosis has taken place the infiltrations will be replaced by ulcers which may be extensive, and may be associated with sloughing of cartilage. Deformity may occur with or without healing. (Stenosis may require tracheotomy or other operations.)

**Case 67.** A thirty-two-year-old white married man entered the Medical Clinic because of hoarseness and "sore throat" of six months' duration. The latter consisted of difficulty in swallowing. Hoarseness had been present for two months before admission. For three months he had noted pain and swelling of both elbows. Motion was limited. His physician had made a diagnosis of tuberculous laryngitis. He had had a chancre twelve years before.

Examination showed evidence of weight loss. The voice was husky. The throat was red and edematous. Examination with the laryngeal mirror disclosed extensive ulceration of the vocal cords and the interarytenoid area. The epiglottis was almost completely destroyed by ulceration. The elbows were swollen, red, and hot. Passive motion was limited. Blood Wassermann and Kahn tests were positive. The spinal fluid examination revealed increased globulin, cells 2 per cu. mm., Wassermann test positive in 1 cc., negative in 0.5 and 0.2 cc., and a negative mastic test. Roentgenogram of the elbow joints showed bone destruction in the humeri.

**Comment.** The occurrence of multiple late syphilitic lesions in a patient is well illustrated in this case. The involvement of the elbow joints was unusual in that on physical examination a pyogenic or gonococcal process was suggested rather than a syphilitic one. Asymptomatic neurosyphilis was present. Under bismuth and iodides the larynx and the joints improved at once.

The first diagnosis by the attending physician is usually chronic laryngitis. However, the diagnosis of chronic laryngitis always demands the elimination of syphilis, tuberculosis, and new growth as the cause of the symptoms. All may closely simulate each other with respect to symptoms, and even upon examination with the laryngeal mirror. Tubercles or tuberculous ulcers of the laryngeal mucosa are almost always attended by symptoms and signs of active and advanced pulmonary disease. Benign papillomas and malignant processes can be diagnosed early only by biopsy. The proof that a laryngeal lesion is of syphilitic origin may require the use of therapy as a test. However, we have seen tuberculous ulcers and laryngeal carcinoma on more than one occasion in patients with latent

**sypylis** If a laryngeal lesion does not begin to involute within two weeks of the beginning of antisyphilitic treatment, further diagnostic studies must be made, including biopsy, to rule out a neoplastic process

#### THE TRACHEA AND BRONCHI

Late sypylis of these structures is exceedingly rare. When it does occur the involvement is usually in the lower third of the trachea, at its bifurcation into the bronchi, or in the main bronchi. From a pathologic viewpoint the lesion occurs probably as a gummatous infiltration of the mucosa which may or may not break down. Scarring takes place in either event. If a breaking down occurs, there is ulceration which may lead to the destruction of some of the cartilaginous rings. Perforation into the mediastinum and its structures has been recorded. Possibly this process may be reversed, and the air passages be involved by disease originating in peribronchial or peritracheal nodes with involvement of the respiratory structures by extension.

**Symptoms** Clinically, these are cough (probably with sputum), and if ulceration is present, probably bloody sputum. With the occurrence of scarring and stenosis, obstructive symptoms may occur, such as dyspnea which may be constant or paroxysmal. Stridor may be present and death may take place in a suffocative attack. The physical signs will consist of decreased expansion of the chest, distant or feeble breath sounds or if stenosis is present, stridulous breath sounds and musical rales.

Sypylitic lesions of the trachea and bronchi are so rare that the use of space for a detailed discussion of the differential diagnosis cannot be justified. A proper history and physical and sputum examinations with the aid, when indicated, of the roentgen ray and bronchoscope will be needed in diagnosis. The differential diagnosis will include a consideration of tuberculosis, bronchiectasis, bronchogenic carcinoma, and extrinsic tumours in the mediastinum, such as aortic aneurysm, lymphosarcoma, Hodgkins' disease, and the like.

#### THE LUNG

Though congenital pulmonary sypylis is a clinical entity commonly recognized, pulmonary lesions of acquired sypylis are very rare, and there is a difference of opinion regarding one type which has been described. From a pathologic standpoint, gumma of the lung in acquired sypylis occurs without question. The so-called fibrotic type, accepted by some clinicians and roentgenologists, cannot be confirmed by the pathologist. Gummata at autopsy have not been found associated with cavitation, but commonly have a radiating fibrosis.

The **symptomatology** consists of cough and sputum with, at times, a low grade fever and weight loss. Examination may not reveal any findings of pathognomonic significance. Roentgenologic study may not be diagnostic. Localized shadows suggesting tumour formation may occur, or there may be a more widespread process resembling an exudative and fibrotic process.

As in syphilis of the trachea and bronchi, such disease of the lung is so rare that it has not seemed worth while to include illustrative case reports in this book. I have briefly described such cases in a paper on the diagnosis in late benign syphilis.

The diagnosis of pulmonary syphilis depends mainly upon the exclusion of other pulmonary diseases by history, physical examination, examination of sputum, and roentgenologic evaluation. Tuberculosis, neoplasm, and silicosis must be considered. Finally, the therapeutic test may give a clue as to the etiology. As indicated above, the rather fine, diffuse fibrotic process which suggests syphilis to some roentgenologists has no pathologic substantiation, and not a very satisfactory clinical background. I am even somewhat dubious about the significance of therapeutic results in more localized lesions. For example, some years ago I observed a middle aged coloured man who had cough and sputum. The roentgenogram revealed a dense shadow several centimeters in diameter in the right lower lobe of the lung. This suggested a tumour. Because of a positive serologic test heavy metal and iodides were given with prompt resolution of the shadow. However, similar shadows are found associated with acute pulmonary disease with subsequent spontaneous resolution.

## SYPHILIS IN THE MEDIASTINUM

If syphilitic mediastinitis is a clinical entity, it is surely very rare. Some clinicians question its existence. It seems probable that if syphilitic disease actually occurs in the mediastinum, it is merely a reaction about a syphilitic focus. There are necropsy reports of *gummata* in the mediastinum involving trachea and esophagus. The reaction about such a focus may conceivably appear on roentgenologic examination as a diffuse infiltration with shadows radiating from the mediastinum. Such a shadow in the syphilitic patient may give rise to the diagnosis of mediastinitis. Resolution of the process following antisyphilitic treatment has been accepted as proving its etiology. At times mediastinitis, resulting in fibrosis, may give rise to obstructive manifestations affecting any of the vital structures lying within the mediastinum.

## SYPHILIS OF THE GASTRO-INTESTINAL TRACT\*

The incidence of gummatous involvement of the gastro-intestinal tract varies with the viscus under consideration. Syphilis of the esophagus is rare, of the stomach not so uncommon, whereas in the liver it is fairly common.

## SALIVARY GLANDS

Gumma of the salivary glands, especially of the parotid gland, has been reported at times. The manifestations are swelling of the glands and increased salivation. Response to antisyphilitic treatment is said to be prompt. Only one such case has occurred in the Vanderbilt University Hospital clinical material.

## ESOPHAGUS

The rarity of gumma of the esophagus is shown by the fact that only some sixty cases have been reported since the beginning of the seventeenth century. From a pathologic standpoint the tertiary lesion appears first as a tumour in the submucosa or in the wall of the esophagus, to go on to ulceration in most instances. According to case reports ulceration apparently may lead to perforation, and even to the formation of a tracheo-esophageal fistula.

**Clinical Picture** Clinically, the picture usually will be that of esophageal obstruction. Increasing difficulty in the swallowing of food, retrosternal discomfort, and loss of weight will complete the picture. The demonstration of the obstruction must be made by barium studies of the esophagus and esophagoscopy.

*The diagnosis of gumma of the esophagus implies its differentiation from carcinoma.* This may be possible only by biopsy and the results of antisyphilitic treatment. A lesion which is not rare—namely, carcinoma of the esophagus—occurs at times in patients with latent syphilis. Therefore, it is obvious that esophageal obstruction in a syphilitic patient does not necessarily mean gumma of the esophagus. (Antisyphilitic treatment may actually cause increased obstruction—the “therapeutic paradox.” The cicatrix produced by the healing of a gumma may result in constriction requiring dilatation.)

## DIAPHRAGM

Gummatous infiltration of the diaphragm in the region of the esophageal hiatus, as a cause of esophageal obstruction, had not been reported previous to our report of three such cases which have occurred at the Vanderbilt University Hospital in the past fifteen years. The gummatous process, by

\* Under this heading I shall also include gumma of the diaphragm, because the symptom complex is referred to the digestive tract.

encroachment upon the lumen of the esophagus, causes obstruction at the level of the diaphragm

The symptomatology is that of esophageal obstruction, of a progressive nature. Roentgenologic studies will reveal obstruction to the passage of barium. Esophagoscopy may reveal narrowing of the lumen without ulceration, as in one of our cases.

**Diagnosis.** Because of the site of the obstruction, the diagnosis will include for differentiation, carcinoma and cardiospasm. Esophagoscopy, roentgenologic examination, and the therapeutic effect of antisyphilitic treatment will be necessary to establish the diagnosis. No case abstracts of gumma of the esophagus or diaphragm have been included here because of their rarity. We have described such cases elsewhere.

### STOMACH

Though gummatous involvement of the stomach is uncommon, it is not so rare as syphilis of the esophagus and diaphragm. The diagnosis of gastric syphilis has been made twenty-six times in the clinics and wards of Vanderbilt University Hospital within the past sixteen years. Pathologists in general seem to be rather loath to accept the increasingly frequent clinical diagnosis of gastric syphilis because of the rarity with which it has been found at the necropsy table. One author indicates his scepticism by saying that there is a great difference between a syphilitic ulcer and an ulcer in a syphilitic. Nevertheless, I believe that many internists of experience are making the clinical diagnosis of gastric syphilis on good evidence and are having it substantiated by the subsequent clinical course. Pathologically the lesion is an unbroken nodule, or a gummatous ulcer, solitary or multiple. Some cases present a diffuse fibrosis. The objection of pathologists to the diagnosis of gastric syphilis is based on the fact that, since the microscopic picture in gummatous ulceration is not pathognomonic, the evidence for syphilis as the etiologic factor is unsatisfactory. Harris and Morgan did isolate the *T. pallidum* from a case of gastric syphilis by rabbit inoculation.

**Clinical Picture.** Clinically, epigastric discomfort or pain is the outstanding symptom. Harris and Youmans, in reporting the first seven cases occurring at Vanderbilt University Hospital, found that abdominal pain was present in all, varying in duration from three weeks to one year. Vomiting occurred in six. The average weight loss was thirty pounds. Examination in these seven cases revealed nothing of especial interest relative to the abdomen except a questionable mass in two. (However, I have treated two cases elsewhere in which in each instance there was an epigastric mass almost the size of an orange. In one of these a mass was visible through the abdominal wall. Treatment was followed by com-



plete disappearance of the mass in each case ) Roentgenologic examination in Harris and Youmans' cases showed the lesion to be prepyloric in four and midgastric in three All had been interpreted originally as being malignant. The gastric analysis in most cases reveals achlorhydria The following case was seen by us subsequent to the report of the cases studied in Vanderbilt University Hospital

FIG 56

FIG 57

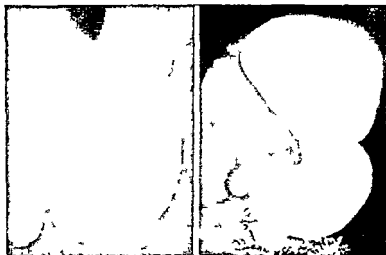


FIG 56 Tertiary syphilis—gummatous ulcer of stomach (Case 68)

FIG 57 "Cure" of gastric syphilis (6 months after beginning treatment) (Case 68)

**Case 68** A thirty two-year-old white man entered the Medical Clinic because of 'gas and fullness of the stomach' of six months' duration. The appetite was good. For four months there had been a dull, aching epigastric pain aggravated by the intake of food. The patient had lost 70 lb. of weight. He gave no history of syphilis. A nine year-old child of his had congenital syphilis.

Examination showed the patient to be emaciated. The abdomen showed no abnormality. A penile scar was present. Gastric analysis showed achlorhydria. Occult blood was present in the stool. Blood Wassermann and Kahn tests were positive. The spinal fluid showed increased globulin, cells 8 per cu. mm., a positive Wassermann reaction in 10, 0.5, and 0.2 cc., and a 4432100000 mastic curve. Roentgenologic study showed a large ulcer on the lesser curvature of the stomach which was interpreted as peptic ulcer.

For experimental reasons the patient was placed on an ulcer regime, without any relief of symptoms. He was then given the routine ward diet, and treated with iodides by mouth and injections of bismuth in oil. The patient rapidly lost his symptoms, he gained 80 lb. of weight within two months. Six months after the first roentgenograms the study was repeated, and showed an absence of any gastric deformity (Figs. 56 and 57).

The diagnosis of gastric syphilis is difficult because the two lesions which must be differentiated from it, peptic ulcer and carcinoma, are much more common in syphilitic patients than is gastric syphilis. The blood tests are usually positive in syphilis of the stomach. In the roentgenologic examination the niche of peptic ulcer is usually not encountered, but rather the deformity of a larger infiltrative lesion. Obstruction is common, and hour-glass deformity may occur. This is seen not infrequently after treatment due to scarring, the "therapeutic paradox." Harris and Youmans set up the following points for the reasonable diagnosis of gastric syphilis: (1) evidence of organic disease of the stomach, which upon roentgenologic examination is indistinguishable from carcinoma, (2) a comparatively young individual, (3) the presence of other evidences of syphilis, (4) a qualified improvement under antisyphilitic treatment, (5) in cases operated upon, demonstration of tissue changes compatible with syphilis. In recent years, gastroscopists have begun to recognize the syphilitic ulcer.

In the treatment of the seven cases reported from our hospital, it was found that two needed surgical intervention after antisyphilitic treatment because of obstruction, and five did well under medical management alone. Six had persistent gastric deformity. Five gained weight. Symptomatic cure occurred in five, and improvement in two.

#### LIVER

Gumma of the liver is the most frequent tertiary lesion occurring in the digestive tract. Some idea of the frequency of tertiary hepatic syphilis can be gained by the number of cases of gumma or its prominent pathognomonic scars one sees at the necropsy table. Osler reported forty-one instances of gumma or scar in 2,300 necropsies at Johns Hopkins Hospital (1.7 per cent). On my coloured male medical service at Charity Hospital in New Orleans, there were seven instances among 279 necropsies (2.5 per cent). Among 168 syphilitics above the age of fifteen years coming to necropsy at Vanderbilt University Hospital, there was one instance of gumma, and one with a scar of past gumma. This condition has been diagnosed forty-one times in the clinics and wards of Vanderbilt University Hospital within the past sixteen years.

The pathologic picture of tertiary syphilis is present in gumma of the liver. Gummata usually begin in the neighbourhood of blood vessels which are thereby destroyed. Usually the lesions are multiple, varying from miliary size to tumours of several inches in diameter. On cut section they are of gray colour. Large ones which have undergone necrosis present yellowish centres. The nodule, unless very small, is usually surrounded by a zone of fibrous tissue. Resolution of the gummata is followed

by deep and extensive scarring because of the rather marked tissue destruction. The dense scars on the surface of the liver may be stellate, or may cut so deeply into the liver parenchyma as to lead to great deformity of the liver. The organ may thus be subdivided into a number of lobes, as it were (*hepar lobatum*). No other disease produces these changes, and therefore such a liver at the necropsy table is considered a signpost that syphilis has passed that way. Rarely, in extensive disease, there may be a fairly diffuse sclerosis, eventually leading to portal obstruction. However, this change is not of the portal cirrhosis type. In passing it may be said that, though in the past syphilis was considered to be one of the possible etiologic factors in portal cirrhosis, most pathologists do not accept this at present.

As the result of better treatment of syphilis in the past decade or more, it appears that less tertiary syphilis of the liver is being encountered. This I believe accounts for the fact that the clinical picture is not recognized so frequently as in the past, even when present. Certainly, how else can one account for laparotomies being done by good surgeons for upper abdominal tumours in the face of blood tests which are positive?

Some patients are asymptomatic, and consult a physician only because of a mass in the abdomen. In some cases portal cirrhosis may be suggested by the slight icterus, ascites, and low grade fever. In other patients the circumstances may suggest tumour of the liver. Epigastric pain and tenderness may be present. The liver may be enlarged and smooth, since no nodules may appear on the surface. More often palpation reveals one or more masses or tumours in the upper abdomen. McCrac pointed out that the left lobe is more extensively involved in a gummatous process than the right. This point may be of importance diagnostically. A friction rub may be heard over the tumour at times. The tumours usually are firm, though I have noted a softer consistency in some, probably due to necrosis. Persistent fever, usually only of one to two degrees, is very common. This is probably due to necrosis within the gummata, similar to the fever found in necrotic neoplasms of the viscera. The spleen may be greatly enlarged in some cases. Anemia is common (Case 69).

**Case 69** A thirty two-year-old white married woman was admitted to the Medical Ward because of a mass in the abdomen. While taking a bath two months before, the patient noted a nontender mass in the right upper abdomen. She was known to have syphilis for seven years. Three years before admission she had had a sore throat which lasted for eleven months.

Examination revealed a constant low grade fever of 1-1.5° was present. The right tonsillar fossa was scarred. The liver was markedly enlarged, and presented on its anterior surface a tumour about 8 cm. in diameter with a smaller one medial to it. (The extent of the liver as mapped out in ink is shown in the

photograph The large tumour is also outlined and is visible as a protrusion and a smaller one is medial to it ) The spleen, as may be seen in the photograph, was also very large Blood Wassermann and Kahn tests were positive

**Comment.** The liver and spleen decreased in size quite promptly under bismuth and iodides The fever disappeared soon after treatment was instituted Of interest is the history of a sore throat which lasted eleven months The

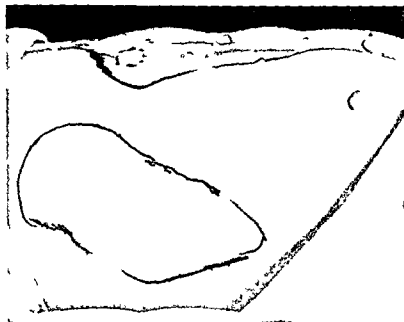


FIG 58 Tertiary syphilis—gummata of the liver, splenomegaly (Case 69)

right tonsillar fossa showed the scar of tissue destruction, a landmark of former gummatous syphilis (Fig 58)

Late syphilis of the liver should be considered in every case of hepatic disease. The blood tests for syphilis are usually, but not always, positive Landmarks of previous gummatous disease are suggestive These may be present as shown in the above case abstract We have seen in other cases the atrophic scars of antecedent tertiary skin lesions The differentiation of hepatic syphilis from the various diseases to be considered very often depends upon the following First, the demonstration that the patient has syphilis, and then the observation of the result of antisyphilitic treatment If hepatic disease is of syphilitic origin, the jaundice, fever, and tumours will show rapid response to treatment However it must be pointed out that, due to residual scarring from previous gummatous hepatitis, *hepar lobatum* may simulate *gumma of the liver* Portal cirrhosis may be simulated especially if there is ascites Probably carcinoma of the liver,

either metastatic or primary, is the most common erroneous diagnosis in gummatous hepatitis because of the presence of tumours in the liver, weight loss, and fever. In several instances I have seen solitary amebic abscess of the left lobe of the liver simulate in all respects a gumma at this site. The tumour and fever occur in both. Amebae commonly are not found in the stool in hepatic amebiasis. Only the failure of antisyphilitic treatment may differentiate the amebic disease from syphilis. Suppuration of the gall-bladder may be considered in some cases, because of fever in the presence of hepatic disease. Hepatic cysts, congenital or echinococcus, may simulate gumma of the liver. The effect of treatment may be, in the last analysis, the deciding factor in the diagnosis of some cases of hepatic disease.

#### PANCREAS

Gumma of the pancreas has been reported as a necropsy finding. Warthin made much of chronic interstitial pancreatitis as a mark of syphilis. Practically, however, this is of no clinical significance.

#### RECTUM

Syphilis of the rectum probably does not occur. The excuse for including a brief statement on this subject is that it was a frequent diagnosis until recent years. The older textbooks of medicine and syphilis mention the supposed entity. At the present time it has been firmly established that the cases of syphilis of the rectum of past years were examples of lymphopathia venereum either in the active stage of proctitis or as a residual stricture. In the class of society in which this disease is common, the co-incidence of syphilis is high, accounting for the errors in diagnosis in the past. In a brief study of the cases of rectal stricture made at Vanderbilt University Hospital, the following was found. Exclusive of those cases of rectal disease in which other etiology was demonstrable, there were sixty-six cases considered ultimately to be instances of lymphopathia venereum. The original diagnoses in these cases were: syphilitic stricture in twenty-seven, benign stricture of unknown cause in twenty-nine, and lymphopathia venereum in ten cases, the latter all diagnosed subsequent to 1936. Fifty-three of the sixty-six cases were in Negroes. Evidence of syphilis was present in 43 or in 63 per cent of the whole group. A number of the old cases were subsequently brought into the clinic for Frei tests and serum-protein studies, and the diagnosis of lymphopathia venereum definitely established.

#### SYPHILIS OF THE GENITO-URINARY TRACT

Renal involvement, occasionally occurring in acute syphilis, was mentioned in the chapter on secondary syphilis. Demonstrable late manifestations of syphilis are rare in the genito-urinary tract.

## KIDNEY

A syphilitic nephrosclerosis has been accepted by some pathologists as an entity. This seems to be open to great question, however. Gumma of the kidney is occasionally found at the postmortem examination. Descriptions have appeared in which such lesions were presumably diagnosed clinically. In some instances because of urinary symptoms, studies have included pyelograms which have demonstrated apparent tumours encroaching on the renal pelvis. Antisyphilitic treatment in some of these patients has led to cure of the symptoms and the disappearance of the pelvic abnormality.

## BLADDER

Ulceration of the bladder has been reported as due to the breaking-down of a gumma of the bladder wall. The symptomatology is that of any chronic ulcerative condition of the bladder.

## TESTICLE AND EPIDIDYMIS

In addition to the occasional case of transient epididymitis which may occur in acute syphilis, late lesions of syphilis are encountered at times in the reproductive organs of the male. Orchitis may be unilateral or bilateral and may have an epididymitis associated with it. The diffuse interstitial form presents a clinical picture of a slow, painless enlargement of the testicle. The organ feels smooth, indurated, and often lacks the testicular sensation. Involution may be followed by atrophy of the gland. Or, the syphilitic process may take a gummatous or nodular form (Case 71). Under such circumstances necrosis, subsequent fistula formation, and ulceration of the scrotum may occur.

**Differential Diagnosis.** Several conditions may have to be considered in the differential diagnosis. Gonorrheal disease of the male generative organs is characterized by pain, fever, and, at times, acute epididymitis in contrast to the more benign process in syphilis. Gummatous disease may simulate tuberculous orchitis and epididymitis. The latter, however, is associated with more pain, and often tuberculous disease can be demonstrated elsewhere. Tubercle bacilli may be found in the urine. Neoplasm of the testicle is much more difficult to differentiate from syphilis, which is especially unfortunate since early surgical treatment is so essential in the former. The malignant process is more likely to be of rapid growth, and may be accompanied by pain. However, neither of these points may be of value in the diagnosis. A therapeutic trial of antisyphilitic treatment will, in the syphilitic lesion, be rewarded with a prompt response shown by beginning involution of the process.

## OVARIES, TUBES, AND UTERUS

Gummatous lesions of these organs have been reported, but are rare. They have been found most often either at operation or at necropsy. Gumma of the uterine cervix may present an indurated ulcer, which may simulate malignancy. Biopsy and the therapeutic test in the syphilitic patient are indicated.

Though demonstrable late lesions in the female reproductive organs are reported with extreme rarity, the physician treating many syphilitics is intrigued by one fairly common observation. Unquestionably syphilis has a profound effect upon the physiology of reproduction in the female. Not uncommonly, the female with apparently late latent syphilis, after four to eight months of antisyphilitic treatment, conceives following even years of sterility. This is so strikingly related to treatment that I do not believe it can be explained on the basis of coincidence.

## PAROXYSMAL HEMOGLOBINURIA

Brief mention will be made of this condition since the patient usually consults his physician because of the urinary findings. Actually the hemoglobinuria is due to hemolysis of red blood cells in the circulation. This syndrome seems to occur in protozoan infections as well as following exposure to certain chemical poisons. Therefore it occurs in spirochetal diseases. Most of the patients presenting this syndrome have positive complement fixation and precipitation tests.

The clinical picture characteristically appears after exposure to cold. A chill and fever, and pain referred to the back and thighs are usual. There may be vomiting and diarrhea. The urine is of port wine colour due to excretion of hemoglobin. A hypochromic anaemia is usual.

## SYPHILIS OF THE LYMPHOID TISSUES

Gummatous involvement of the lymph nodes is a very rare manifestation, in striking contrast to the almost universal reaction in lymphoid structures during the early stages of the disease. A generalized shotty adenitis may remain as a residuum of the early lymphadenitis.

Gumma of the lymph node presents as a tumour of a lymph node which may or may not break down. At times such lymphadenitis may, by its position, lead to a bizarre circumstance, as occurred in one case I had the opportunity to see at laparotomy. Here obstructive jaundice was due to a gummatous lymph node pressing upon the common bile duct.

The rare case of gumma of a lymph node will need to be differentiated from tuberculosis or other chronic infections, Hodgkin's disease, and primary and metastatic tumours of lymph nodes.

Splenic involvement in tertiary syphilis as an isolated condition is rare. Gumma of the spleen was found once in one hundred and sixty-eight patients with syphilis coming to necropsy at Vanderbilt University Hospital. Not unusually there may be splenomegaly associated with gummatous hepatitis, as was shown in Case 69. Splenic anaemia (Banti's syndrome) has been related to syphilis in a few cases. Presumably syphilitic vascular disease might be a factor in the production of this syndrome when considered in the light of the newer concepts of this syndrome.

## SYPHILIS OF THE BLOOD-FORMING ORGANS

Though it may be granted that the systemic infection of secondary syphilis, just as in any other infectious process, can produce some degree of anaemia, the probability of this occurring in late syphilis is not likely. Some syphilologists believe that a secondary anaemia (hypochromic) may be a manifestation of late syphilis, especially in women. I believe this is open to question. Certainly in the economic strata which contribute so greatly to our syphilis clinics hypochromic anaemia is exceedingly common. If one will forget the syphilis clinic for the moment and consider the medical clinic, one is struck by the high incidence of hypochromic anaemia there. This is especially true in women in whom, in addition to poor nutrition, there are such potent factors as repeated pregnancies, menstruation, and prolonged periods of lactation.

## SYPHILIS OF GLANDULAR TISSUES

### LACRIMAL GLAND

The lacrimal gland is an exceedingly uncommon site of late benign syphilis. Involvement of this structure is characterized by painless swelling of the lacrimal gland, ptosis of the upper lid, and exophthalmos. One such case has appeared among the clinical material of the Vanderbilt University Hospital Syphilis Clinic.

### BREAST

Gummatous involvement of the breast is occasionally reported.

## SYPHILIS OF THE SKELETAL SYSTEM

Tertiary syphilis of bone may be as frequent, if not more so, than late syphilis of the skin. I feel that the frequency is greater than is generally believed. It is difficult to confirm this belief for several reasons. The roentgenologic demonstration of bone syphilis depends upon at least a moderate degree of bone change. However, it has been the experience of every one who has treated much syphilis to encounter many instances of



bone pain in patients in apparent late latency which was relieved by anti syphilitic treatment. The roentgenogram usually shows no bone changes in these instances. Indeed, in some of these cases where the bone is not covered by much overlying tissue, one may even be certain of swelling, irregularity, and tenderness of the periosteum. Very commonly syphilis of bone occurs at multiple sites. Not infrequently the roentgenogram reveals changes at one site and none at another, though pain may have been referred to both.

From a practical viewpoint many of us are restricted to some extent in the use of roentgenograms in diagnosis. If only one site can be chosen for roentgenologic examination, the best one may not be selected, and the report may thus be negative, whereas another site might have shown a bone lesion. I therefore believe that we must accept the probability that some degree of bone involvement is quite common in late syphilis though the support for this impression rests upon subjective changes resulting from treatment rather than upon the objective evidence of the roentgenogram.

#### FREQUENCY AND DISTRIBUTION

In 561 cases of late benign syphilis in the Vanderbilt University Hospital Syphilis Clinic, there were 161 diagnoses of bone syphilis. A detailed study has been made of 106 of these cases in which either the clinical picture or the roentgenologic examination seemed to establish the diagnosis. The distribution of these cases as to race and sex is as follows: 20 cases each occurred in white males and females, 31 cases appeared in Negro men, and 35 in Negresses. Most of the cases fell into the fourth and fifth decades of life, though there were numerous examples in the third decade. In the 43 patients who gave a history of syphilis, the infection had been present from 5-20 years in 31, the remainder having either a shorter or longer duration.

#### PATHOLOGIC PICTURE

Though the pathology of tertiary syphilis has been discussed earlier in the chapter, reconsideration of this as related to bone may be of interest. The pathologic picture of bone syphilis assumes one of two forms—gummatous involvement of the periosteum, or gummatous osteitis. In the former there is a perivascular inflammatory infiltration of round cells. This may rupture through the periosteum to form an ulcer of the skin if the bone is near the skin, exposing the underlying necrotic bone, or there may be no ulceration, and instead new bone formation may appear on the surface of the old cortex. This overgrowth accounts for the rough, irregular thickening which may occur on the long bones—as over the tibia, for example. In other instances this overgrowth may extend inward

along the haversian system into the depths of the bone, thus the shaft of the bone is dense and ivory like

The second type of process, *gummatous osteitis*, is destructive. It may begin in the periosteum and extend into the bone as a perivascular gummatous inflammation, eroding the haversian canals and producing a "worm eaten" appearance. Confluence of this process may produce extensive

FIG 59

FIG 60



FIG 59 Tertiary syphilis—per chondritis of nasal septum (Case 70)

FIG 60 Therapeutic paradox following treatment (Case 70)

destruction of bone. Examples of *gummatous osteitis* are seen at their best in the flat bones, though such lesions may occur also in long bones. In addition to these two characteristic types of pathologic change, there may occur another. Gumma formation in the marrow cavity may erode the cortex from the inside, and simulate osteomyelitis of other than syphilitic etiology. Furthermore, in the skeletal system, syphilitic inflammation and granulation tissue may affect bursae, joints, and tendon sheaths. This may cause serous exudates. In these instances there is often syphilitic disease of adjacent bone, as in the epiphyses, for example.

*Perichondritis* may occur in cartilage as does *periostitis* in bone. This may be seen in the costal cartilages, the ear, and cartilaginous nasal septum (Case 70).

**Case 70** A thirty-one year-old white man entered the Medical Clinic because of a 'sore of the nose'. Fifteen months before he had had a penile lesion followed by a rash. He received fifteen injections of neoarsphenamine, and five

of bismuth Nine months later he fractured his nose and healing had not taken place

Examination showed that the nasal septum was perforated in its bony part The tip of the nose was swollen, purplish red in colour, but was not hot or tender The nares contained crusts Four crusted skin lesions varying from 0.5-1 cm in diameter were found upon the trunk Blood Wassermann and Kahn tests were positive Spinal fluid examination revealed increased globulin, 15 cells per cu mm, positive Wassermann reaction in 1.0 and 0.5 cc, negative in 0.2 cc with a negative mastic test

**Comment** This case illustrates precocious tertiaryism, in that a destructive lesion developed upon the site of trauma early in the course of syphilitic infection This began as perichondritis of the cartilaginous septum, or as a cutaneous lesion, probably the former Under treatment there was complete destruction of the cartilaginous septum ("therapeutic paradox") with resulting closure of the nares which was almost complete After a year of treatment a plastic operation restored the nose satisfactorily Asymptomatic neurosyphilis was also present (Figs 59 and 60)

From the clinical viewpoint, any bone of the body may be involved by a syphilitic process and give rise to symptoms and signs Table XXI gives the distribution of bone lesions in 106 of the cases of bone syphilis at Vanderbilt University Hospital Involvement of the bony nasal septum, with subsequent perforation, is so frequently associated with other late manifestations of syphilis that the diagnoses have not been recorded as they should have been in our clinic Since the recorded figures would be inaccurate, they have not been included in this table

#### SYMPTOMS AND SIGNS

Syphilis of skeletal structures may give rise to a number of symptoms and signs It may be quite impossible to differentiate pure periosteal involvement from that associated with gummatous osteitis, except by the use of the roentgenogram This is to be expected, for it is difficult to think of osteitis without involvement of the overlying periosteum Such can occur only in gumma of the marrow cavity Trauma is probably a potent factor in the determination of the site of syphilis of bone

Pain is the most frequent symptom bringing the patient to the physician This may be especially accentuated at night, though I suspect this feature has been somewhat overemphasized Swelling of the part occurs commonly, and this may be so firm as to suggest a bony tumour A complaint of tenderness of the involved bone and stiffness of adjacent joints is common Weight loss was quite common in our cases, reaching as much as forty five pounds in one case

Examination often reveals striking tenderness Swelling of the extrem-

ity, tumour, and limited motion are commonly found. In involvement of either the periosteum only, or with underlying bone, ulceration of the overlying skin may occur. This occurs at sites where the skin lies close to bone, as over the tibia. Sinuses may form connecting with cavities in the bone (Case 59). Table XXII indicates the types of symptoms and signs met with in our 106 cases of bone syphilis.

TABLE XXI

DISTRIBUTION OF PROBABLE BONE LESIONS IN LATE SYPHILIS (106 CASES)

<i>Bones</i>	<i>Periostitis (Roentgeno- grams) 10 Cases</i>	<i>Gummatous Osteitis (Roentgeno- grams) 36 Cases</i>	<i>Condensing Osteitis<sup>1</sup> (Roentgeno- grams) 8 Cases</i>	<i>Bone Syphilis; Clinical Diag- nosis; Roent- genologic Examinations Not Done or Negative 52 Cases</i>
Cranium .	—	9	—	6
Maxilla .	—	1	—	—
Mandible .	—	1	—	—
Clavicle .	1	4	1	12
Sternum .	2	2	—	3
Ribs .	—	2	—	—
Scapula .	—	3	—	—
Vertebrae .	—	1	—	—
Pelvis .	—	1	—	1
Humerus .	—	5	—	5
Radius-ulna	—	1	—	7
Femur .	2	4	—	5
Tibia .	4	14	8	18
Fibula .	—	2	3	4
Bones—foot	1	—	—	—
Totals .	10	50	12	61

<sup>1</sup> In the thirty-six cases in which there was roentgenologic evidence of gummatous osteitis, all bones thought to be affected were not studied by roentgenograms because of the expense. But one or more bones in each case were shown to contain a destructive process.

Roentgenologic examination may be of assistance in the diagnosis. The experienced roentgenologist is able to recognize the lesions of tertiary syphilis. In light of the pathology described earlier, the roentgenologic findings are readily understood. The periosteal reaction will be represented by increased density overlying the surface of the bone. Gummatous

osteitis, a destructive process, produces a "moth-eaten" appearance, seen at its best in the flat bones—as the skull, for example. Occasionally the overgrowth of new bone produces a shadow of increased density—condensing osteitis. Cases 67, 71, 72, and 73 demonstrate some of the characteristic clinical findings in bone syphilis.

TABLE XXII

SYMPTOMS AND SIGNS IN 106 CASES OF SYPHILIS OF BONE

		<i>Number of Cases</i>
<i>Symptoms</i>		
Pain		79
Swelling		56
Nocturnal pain		42
Bony tumour		31
Stiffness		26
Tenderness		20
Trauma		17
Local heat (increased)		11
Redness		7
Immobility		3
Drainage		13
		<i>Number of Cases</i>
<i>Signs</i>		
Tenderness		80
Swelling		55
Multiple sites		53
Tumour		48
Limited motion		22
Redness		15
Heat		13
Sinus		8
Ulcer		4

**Case 71** A fifty-seven year-old white man complained of a 'lump' on the chest. Three months before admission he noted swelling over the sternum and of the left sternoclavicular joint, which gradually increased in size. A nodule of unknown duration had been noted in the right testicle. He gave a history of having a chancre six years before.

Examination revealed a large soft mass, which did not pulsate, present over the midsternum. A smaller one was present at the left sternoclavicular joint. It contained a sinus from which drained a serous fluid. In the posterior portion of the right testicle was a hard walnut sized nodule. Roentgenologic examination of the sternum in a lateral view showed roughening of the sternum. Blood Wassermann and Kahn tests were positive.

**Comment** At first glance the mass of the chest wall might suggest an eroding aortic aneurysm. However, there was no pulsation. The sternum is a favourite site of gummatous osteitis, which may break down with drainage, and a subsequent depressed scar. The frequent multiplicity of tertiary lesions is well illustrated in this case. Both bone lesions and the testicular gumma subsided on the use of iodides and bismuth. A scar was the only residuum marking the



FIG. 61 Tertiary syphilis—osteitis of the sternum and clavicle (Case 71)

sinus of the sternoclavicular region. A pea sized nodule marks the site of the former gumma of the testicle (Fig. 61).

**Case 72** A thirty-one-year-old white man entered the Surgical Clinic because of severe headache. Six months before he fell from a truck, striking his head. He was unconscious for five minutes. Three months before admission he had had a three week period of constant and severe headache. This symptom recurred in the few weeks before admission, vomiting was frequent during this time. He has a history of having had a penile chancre six years before.

Examination revealed questionable nystagmus. The skull was tender. Blood Wassermann and Kahn tests were positive. The spinal fluid was negative. Roentgenogram of the skull showed destruction of the outer table of the occipital bone and a like area in the frontal bone.

**Comment** Because of the previous trauma, it was thought that this patient might have a subdural hematoma. The roentgenologist made the diagnosis of syphilis. The serologic proof was obtained later. Under antisyphilitic treatment there was rapid improvement of the symptoms (Fig. 62).

**Case 73** A thirty-six year-old Negress entered the Medical Clinic because of anorexia, abdominal discomfort, and a loss of 54 lb in weight during the preceding two years. Aching had been present in several joints for some months, with pain and swelling in the right leg for four months. For a year there had been a 'swelling' on each side of the forehead, the one on the left side having drained for four months before admission to the clinic. There



FIG. 62 Tertiary syphilis—osteitis of the skull (Case 72)

was no history of syphilis. Her blood was said to have been negative some months previously.

Examination disclosed that the patient was an undernourished Negress with evidence of weight loss. An egg sized tumour was present in the right fronto-parietal region at the hairline. There was a draining sinus at a similar site on the left. The lower half of the right leg was markedly swollen so that the skin was shiny, and exquisitely tender to touch. The liver was enlarged. Blood Wassermann and Kahn tests were positive. Spinal fluid was negative. Roentgen ray examination revealed a 'moth-eaten' appearance of several areas in the skull. A similar lesion was present in the right fibula. There was some osteitis and periostitis in the tibia.

**Comment** The frequent multiplicity of tertiary lesions is well shown in this case. Improvement was prompt following therapy with iodides and bismuth.

Gain in weight was rapid. She remained "Wassermann fast," but later became negative spontaneously. The roentgenogram shows the osteitis of the fibula as well as of the tibia. The periostitis is illustrated by the elevation over the area of osteitis (Fig. 63).

Multiple foci of bone disease are frequent. Table XXII of symptoms and signs indicates that about one-half of our cases had more than one



FIG 63 (Lateral and anteroposterior views) Tertiary syphilis—periostitis of tibia and gummatous osteitis of fibula (Case 73)

focus. In cases of bone syphilis, other tertiary lesions may be found as well. One-fifth of our cases had additional diagnoses of late clinical syphilis including: late skin syphilids in 11, cardiovascular in 5, neurosyphilis in 5, syphilis of the larynx in 1, and of the testicle in 1. Spinal-fluid examinations in 40 patients showed 11 to be seropositive.

#### DIAGNOSIS

The diagnosis of syphilis of bone is not difficult if the condition is kept in mind. Presented with a clinical picture which includes some of the above symptoms and signs, the physician who thinks of syphilis will direct his questions in an attempt to bring out a history of infection. Serologic tests are obviously of great value. They are almost always positive. In



only one of the 106 cases in our series were both Wassermann and Kahn tests negative. In all others at least one or the other was positive. The Kahn test was positive in 98 cases, the Wassermann in 88. In the event of either a history of syphilis or positive serologic tests, a therapeutic trial with heavy metal and iodides will settle the diagnosis within a few weeks. Improvement is usually rapid. The roentgenogram is often of great assistance in making the diagnosis. However, it may be negative even in the presence of pain, swelling, tenderness, tumour, and rapid response to treatment as was true in a number of our cases (Case 75). Therefore negative roentgenologic findings do not rule out syphilis of bone.

Several conditions must be differentiated from bone syphilis under certain circumstances. **Syphilitic meningitis** may need to be considered in a syphilitic patient having constant headache. In the absence of a tumefaction, the roentgenogram and spinal fluid examination will be necessary to establish the diagnosis. However, asymptomatic neurosyphilis may be present in addition to osteitis of the skull. Persistent and severe headache may suggest brain tumour. The roentgenologic and serologic examinations may point the way to the diagnosis of syphilis, and a trial of treatment will soon establish the diagnosis. Metastatic carcinoma or multiple myeloma of the skull may be difficult of differentiation from a roentgenologic as well as a clinical viewpoint. The roentgenologist's opinion, the blood tests for syphilis, a search for a primary malignant focus, examination for Bence-Jones protein in the urine, and a trial of antisyphilitic treatment may be necessary in the differential diagnosis.

In syphilis of the bones of the face we have encountered such diagnoses as carcinoma of the antrum, empyema of the frontal sinuses, retrobulbar tumours (of the eye, with exophthalmos), and osteomyelitis. The diagnosis of these may seem to be confirmed by roentgenograms. Only the positive blood tests may give the clue. Osteitis of the bony nasal septum with perforation is a common landmark of syphilis. However, the clinician must remember that operation on the septum, foreign bodies, chromium poisoning, and picking at the nose may lead to perforation.

**Periosteal or bone syphilis of the clavicle and sternum** are not uncommon. Involvement of the sternoclavicular joint (Case 71) may suggest arthritis, especially gonorrheal, though the latter usually is accompanied by greater evidence of acute inflammation. Gummatous osteitis of the sternum often presents a tumefaction suggestive of an aortic aneurysm eroding the chest wall. The absence of pulsation almost certainly rules out an aneurysmal sac. Syphilis of ribs clinically may suggest bone tumour.

**Syphilitic periostitis of long bones** must be differentiated from nonsyphilitic periostitis, as from trauma, scurvy, and the like. Ulcers over

the tibia at times raise the question of etiology—whether due to syphilis, varicose veins, or stasis. Gummatous osteitis of long bones must be differentiated from tuberculous and pyogenic osteomyelitis. When the involvement is in the marrow cavity, pyogenic osteomyelitis can be simulated very closely. Syphilis may produce bone lesions which are almost indistinguishable from tumours of bone, not only clinically but also roentgenologically. In two instances in our cases biopsies were done in spite of positive blood tests because of the roentgenologic diagnosis of tumour.

Syphilis of the small bones of the hands and feet, as well as involvement of larger bones adjacent to joints, may simulate quite closely one of the various arthritides—rheumatoid, tuberculous, gonococcal, and gouty.

In the differentiation of the various diseases of the skeletal system mentioned above, the diagnosis must rest upon careful history taking, physical examination, serologic tests for syphilis, and roentgenologic study. As was noted above, the latter may offer no assistance, whereas the blood tests are almost always positive. But the syphilitic patient in the latent stage also commonly suffers from nonspecific disease of the skeletal system. Therefore in the last analysis, a test of antisymphilitic treatment often makes the diagnosis. With iodide and heavy-metal treatment, changes appear quite promptly. By the time the patient has had two or three injections of bismuth the pain, tenderness, and swelling have begun to decrease. Progressive improvement is continuous. Months may elapse, however, before much recalcification is demonstrable on roentgenograms in the case of bone defects. Eventually the restoration may be so good that the former site of bony destruction can no longer be identified.

#### HYDRARTHROSIS

Hydrarthrosis, an occasional late manifestation of syphilis, was mentioned in the paragraph on pathology. Several such instances, with involvement of the knee joint, have appeared among the Vanderbilt cases. The condition occurs most frequently in the knee joint. In the absence of known trauma or an acute infectious process, a swelling of the joint develops which is maintained for months or years. It is entirely unassociated with pain, and may merely bother the patient from a mechanical standpoint. Upon examination the joint capsule is found to be distended, and the fluid content of the joint may be demonstrated by ballotment of the patella. There is no tenderness, warmth, or much limitation of movement. The roentgenogram usually shows no bone involvement (Case 74).

Case 74. A fifty-seven year-old Negro house boy was admitted to the Medical Clinic because of swelling of the knee. This had been present for four

months, was painless, nontender, and interfered with activity only slightly in a mechanical way. There was no history of previous trauma or of syphilis.

Examination showed a nontender swelling of the right knee. Joint motion was free. A large amount of fluid could be demonstrated in the joint. Blood Wassermann and Kahn tests were positive. Roentgenologic study was negative. The patient refused treatment, and returned twenty-six months later. The con-



FIG. 64 Tertiary syphilis—hydrarthrosis (Case 74)

dition had changed in no way from the previous examination. Blood Wassermann and Kahn tests were positive. Spinal fluid was negative. Roentgenogram showed a minimal amount of periostitis of the femur.

**Comment.** Painless hydrarthrosis not due to trauma should always suggest syphilis. The joint enlargement quickly subsided under treatment with iodides and bismuth. After the fluid had disappeared some swelling and re-accumulation of fluid at the end of the day was noted. The use of an elastic knee support for a few weeks permitted the tissues to recover their tone. The support was then discarded without any recurrence of fluid in the joint (Fig. 64).

From a diagnostic point of view, a large joint in a syphilitic patient might suggest Charcot joint, due to tabes dorsalis. However, this is quickly

ruled out by the presence of effusion without crepitus, the lack of abnormal mobility, the absence of central-nervous-system disease and absence of bony enlargement

### SYPHILIS OF SKELETAL MUSCLE

Gumma of skeletal muscles is rare. The patient becomes aware of gradually enlarging tumefaction in the muscle, which may be attended with some discomfort. These masses may break down to form fistulae (Case 75).

**Case 75** An eighteen year-old white boy entered the Surgical Ward because of tumours of the legs. He bruised his left leg six months previously in a fall from his bicycle. A month later a nonpainful red swelling was noted at the site of injury at the ankle. Three months before admission he became aware of a mass in the left calf muscles. There was no history of acute syphilis nor sexual exposure.

Examination showed that there were no stigmata of congenital syphilis. The left leg showed two large nontender firm masses. One was the size of a hen's egg, and apparently in the belly of the gastrocnemius muscle, the other laterally just above the ankle. Blood Wassermann and Kahn tests were positive. The spinal fluid was negative. Roentgenogram of the left ankle and leg revealed no bony pathology.

On the Surgical Ward he received iodides, and was given neoarsphenamine 0.2 Gm  $\times$  1. He was referred to the Syphilis Clinic. The tumours had disappeared by the time of the fourth treatment. He received neoarsphenamine 0.6 Gm  $\times$  44, and bismuth  $\times$  34, in a two-year period. He remained "Wassermann fast." Upon his return to the clinic two years after cessation of treatment, the blood tests had reversed, and to our knowledge remained so for ten more months.

**Comment** The mass in the gastrocnemius muscle was unquestionably a gumma. The mass at the ankle probably had its origin in the tendon sheath. The relationship of trauma to gummatous involvement is shown in this case.

In gumma of skeletal muscle differentiation must be made from new growth such as sarcoma. A positive blood test for syphilis and involution of the lesion under antisyphilitic treatment will settle the diagnosis.

### SYPHILIS OF THE EYE

Consideration has already been given to the iritis or iridocyclitis, and chorioretinitis which may occur in the secondary stage of syphilis or as a relapse phenomenon. We must briefly repeat the discussion of this manifestation, since it may be definitely a late condition, and since certain treatment difficulties may occur in the late case. Among 561 cases of late benign syphilis diagnosed in our clinic were 54 instances of involvement of the eye.

## IRITIS

In the iritis of late syphilis, as in early syphilis, the symptoms are those of photophobia, pain, and dimness of vision. Examination of the eye reveals the violaceous circumcorneal injection, the edematous iris, and usually a small pupil, in places there may be adherence to the anterior lens capsule. Steaminess of the cornea often is associated with iritis, thus constituting actually a kerato-iritis. Case 76 illustrates iritis as a late manifestation, and its refractoriness to treatment. The latter point is also brought out in Case 90.

**Case 76.** A twenty-nine-year-old Negress was admitted to a hospital for a hysterectomy. While there she was found to have a positive blood test, and was given an injection of neoarsphenamine. Within two or three days she noted pain in the eyes, photophobia, lacrimation, and impaired vision. She received several more injections without any improvement. After her discharge she received neoarsphenamine 0.6 Gm  $\times$  8 at weekly intervals. Since no improvement occurred she was referred to the Vanderbilt University Syphilis Clinic for consultation. The history indicated that syphilis had been present for a number of years.

Examination revealed that the corneae were cloudy. There was a violet-coloured circumcorneal injection, the pupils were dilated due to the use of atropine by her physician. Blood Wassermann and Kahn tests were positive.

Because of the lack of response to prolonged and full dosage of neoarsphenamine, the patient was treated with arsphenamine in 0.4-Gm dosage. The eye symptoms and signs had completely cleared up after two injections of the drug. After ten injections of arsphenamine, the patient was returned to her physician, who carried out continuous treatment with bismuth and neoarsphenamine without subsequent relapse.

**Comment.** Though the exact duration of the disease was not known, there were reasons to suspect a rather long duration. The stubbornness of the lesion to treatment as well as "Wassermann fastness" which persisted for a long time bore this out. This case demonstrates the not unexpected resistance to treatment with the more common arsenicals, and its prompt response to arsphenamine. The onset of iritis in this case probably represents a Herxheimer reaction.

## CHORIORETINITIS

Chorioretinitis is a gummatous infiltration of the choroid coat of the eyeball. Symptomatically, there is progressive loss of vision. Examination of the ocular fundus reveals either the active stage of the disease, or more often a combination of this with residuae due to involution of some lesions. The active foci are seen as areas of white exudate in the retina. These vary in size and number. Opacities in the vitreous humor may also be present. The residuae following disappearance of the retinal exudate appear as white

patches surrounded by black pigment. The white area represents the sclera as it appears through the atrophied choroid and retina (Case 77).

**Case 77.** A twenty-nine-year-old white male complained of sudden onset of dimness of vision six weeks before. This progressed rapidly for four days to such a point that vision was limited to the recognition of the presence of large objects at short distance. Subsequently visual impairment progressed slowly. Several "blood tests" had been done before he came to Vanderbilt University Hospital and were said to be negative. He had had acute syphilis seven years before.

Examination disclosed that perforation of the bony nasal septum was present. Ophthalmoscopic examination showed scattered patches of white exudate and many pigmented scars in both retinæ. Blood Wassermann and Kahn tests were positive repeatedly.

To avoid a Herxheimer reaction with greater loss of vision, the patient was saturated rapidly with bismuth by using a water-soluble salt every third day. After three injections, neoarsphenamine 0.15 Gm. was given without untoward reaction. This was followed at three-day intervals by 0.3 and 0.45-Gm. doses, after which 0.6-Gm. doses were used weekly.

**Comment.** Though syphilis had been suspected as being the cause of chorioretinitis in this patient, negative blood tests in the laboratories used deterred physicians from using antisyphilitic treatment. Improvement was rapid under specific therapy, and soon vision was so restored that the patient could read the fine print of a newspaper unaided by lenses. No relapse occurred.

There is nothing about either iritis or chorioretinitis which is characteristic of syphilis. Therefore the differentiation of these lesions from those due to tuberculosis, gonorrhea, rheumatic fever, and focal infection must depend upon a careful history, physical examination, laboratory data, and the effect of therapy.

(Other eye involvement such as neuroretinitis and primary and secondary optic atrophy will be considered in the chapter on neurosyphilis.)

## SYPHILIS OF THE DUCTLESS GLANDS

Cases of syphilis of endocrine glands have been reported. Probably no clinician will be fortunate enough to see an example of each of these. Involvement of the endocrine system emphasizes the oft-made remark that syphilis is a disease which may involve every tissue of the body.

### THYROID GLAND

Syphilitic thyroiditis, as gumma of the thyroid gland, has been occasionally reported.

### PITUITARY GLAND

Simmond's disease, a syndrome associated with disease of the anterior lobe of the pituitary gland, has been reported due to syphilis.

## ADRENAL GLAND

Though concomitant syphilis has not been so uncommon in cases of Addison's disease, its relationship to this syndrome is probably merely coincidental. However, gumma of the adrenal gland has been reported. Warthin reported that the microscopic features of syphilitic inflammation frequently appear in the adrenal glands.

## · TREATMENT OF LATE BENIGN SYPHILIS

Some general remarks will be made relative to the treatment of tertiary syphilis, following which a plan of treatment will be outlined. Because of peculiar circumstances, this treatment will be amplified with respect to certain of the late manifestations of syphilis.

In the consideration of treatment in late latent syphilis, the Herxheimer reaction was discussed. Knowledge of the possibility of such a reaction in late syphilis is essential in the proper management of the patient. *The use of arsenicals, in the patient unprepared with heavy metal and iodides, in the presence of tertiary lesions may be dangerous.* Admittedly a Herxheimer reaction in the tertiary lesions of skin and bone will not be of serious consequence. In the latter, pain may be temporarily intensified because of an increased inflammatory reaction in tissue that cannot expand. Some syphilologists use arsenic at once in cases of late benign syphilis of skin or bone.

I should like to ask the reader to review the examples of late syphilis described in this chapter. He will be struck by the number of cases in which there is evidence of multiple late lesions. This means that the patient with a gummatous reaction in one tissue may have the same in another where a Herxheimer reaction might be dangerous. Such reaction in tertiary syphilis of the larynx is associated with swelling and edema. Perforation in gastric syphilis has been reported following the use of arsenic without preparation of the patient with bismuth. Intensification of the manifestations of tertiary syphilis of the liver may occur with impairment of liver function, and may conceivably lead to acute yellow atrophy. The latter has been reported. The reaction in chorioretinitis may lead to increased impairment of vision because of intensification of the retinal reaction.

Even though the Herxheimer reaction is not of a dangerous degree, it may bear a definite relationship to the amount of scar in healing or the so-called "therapeutic paradox" which was discussed in Chapter v. The "therapeutic paradox" is demonstrated best in syphilis of a hollow viscus. For example, very commonly following treatment in gastric syphilis the

resulting scar produces an hour-glass deformity of the stomach which requires subsequent operation because of obstructive symptoms. It will appear obvious to the reader that if there is intensification of the inflammatory process at the gummatous focus due to the use of an arsenical, necrosis or tissue destruction will be accentuated. Thus the "therapeutic paradox" may be greater than if resolution occurred more slowly as the result of preparatory therapy with iodides and a heavy metal.

The foregoing considerations thus lead to a general rule which is always safe for the practitioner. *In a patient with late benign syphilis, never begin treatment with arsenicals. Initiate treatment with a course of heavy metal and iodides.* By following such a plan the possibility of a Herxheimer reaction will be reduced to the minimum. Involution of the lesion will occur with the least possible reaction in the gummatous focus, and the degree of the "therapeutic paradox" will be kept at a minimum. The effectiveness of bismuth and iodides in late benign syphilis will be beautifully demonstrated to the physician if he will but keep close watch on the involution of the tertiary lesions of the skin and mucous membranes. *Similar results obtain in the nonvisible lesions within the body.*

As was noted earlier in this chapter, a certain number of the patients having late benign syphilis also have cardiovascular or central nervous system syphilis. (Spinal fluid examination is essential in every case of late benign syphilis.) Under such circumstances the plan of treatment must be directed to the management of these more serious lesions, with the treatment of the benign lesion being coincidental.

The very fact that this discussion of treatment concerns the management of late benign syphilis implies that, in general, the patients belong to an age group older than that in which acute syphilis usually occurs. Therefore a higher incidence of coexistent disease will be encountered. The presence of one or other of the degenerative diseases may force the physician to extreme conservatism in the use of antisyphilitic treatment. In his enthusiasm for the active treatment of syphilis, and in an attempt to produce a negative serologic test in the patient, the physician often loses his perspective of the effect of syphilotherapy upon the host. Certainly, it is pointless for the physician to so manage the patient that the treatment is of greater danger than the disease. *Individualization of treatment is thus essential.*

The objective of antisyphilitic treatment in late benign cases is not "cure," but (1) to attain resolution of the existent tertiary process and the relief of symptoms attendant to it, (2) to allow as great a restoration of normal structure and function as possible, and (3) to prevent subsequent gummata. Therefore it is the belief of some syphilologists that in many instances the use of heavy metal and iodides only is sufficient.



Under such circumstances heavy metal is given in courses with intervening rest periods.

However, Wassermann and Goodman, at the Johns Hopkins Hospital Syphilis Clinic, have shown that if cases of late benign syphilis receive no more treatment than that outlined for late latent syphilis, 13 per cent may have a relapse of the late lesions. They therefore recommend from five to seven courses each of arsenic and bismuth (eight injections per course) on a continuous treatment plan.

#### GENERAL TREATMENT

This general principle of treatment is followed at the Vanderbilt University Hospital Syphilis Clinic with the following modifications. In order to avoid Herxheimer reactions, we begin treatment with at least four weeks of bismuth before neoarsphenamine is used. Subsequent to this introductory bismuth course continuous treatment is carried out consisting of alternate courses of bismuth and arsenic over a period of about two years. In the third year, following a three months' rest period, a course of twelve injections of bismuth is given. Potassium iodide is given for the first month or two of treatment, and subsequently in association with the next several bismuth courses. Neoarsphenamine should be used in moderate dosage. For a case in which 0.6 Gm. would be the dosage of choice in acute syphilis, 0.45 should be sufficient in late benign syphilis. Arsenoxide may be used in a 0.06-Gm. dosage. Table XXIII offers a treatment scheme for use in late benign syphilis.

As was indicated before, individualization of treatment is insisted upon in our clinic. Obviously it is impossible to cover all the possible contingencies which might arise to alter the above general outline. However, some of these are noted below.

#### CONTINGENCIES WHICH MAY CONTRAINDICATE GENERAL TREATMENT

Age may indicate that a more conservative course of treatment should be followed. In an aged patient with tertiary lesions of skin, mucous membrane, or bone, it is apparent that relief of symptoms is all that is needed. Under such circumstances iodides and weekly injections of bismuth for 10-12 week courses alternating with 8-12 week rest periods may be sufficient. Such treatment may be carried out over the period of a couple of years. In the event of emaciation or undernourishment in the aged, the gluteal muscles may be so atrophic that bismuth cannot be given without untoward results. Therefore the use of mercury inunctions may be indicated.

Coincident disease, such as malignancy and advanced arteriosclerotic or hypertensive heart disease, is not infrequent in our clinic

TABLE XXIII

SCHEDULE FOR TREATMENT OF LATE BENIGN SYPHILIS<sup>1</sup>

<i>Time in Weeks</i>	<i>Drug</i>
4	Bismuth in oil, weekly
8	Neoarsphenamine, weekly
8	Bismuth in oil, weekly
8	Neoarsphenamine, weekly
8	Bismuth in oil, weekly
8	Neoarsphenamine, weekly
10	Bismuth in oil, weekly
6	Neoarsphenamine, weekly
10	Bismuth in oil, weekly
6	Neoarsphenamine, weekly
10	Bismuth in oil, weekly
6	Neoarsphenamine, weekly
12	Bismuth in oil, weekly
12	Rest
12	Bismuth in oil, weekly
Total 128	Totals Arsenic 42, Bismuth 74

<sup>1</sup> For dosage, see Chap. v

in the cases of late syphilis of skin or bone. Here also the management, in my opinion, should be similar to that mentioned above.

**Tertiary syphilis of the liver** may call for a slightly different plan of treatment than the general one outlined for late benign syphilis. In the case of large gummata of the liver, I am sure that resolution is not complete in four weeks of bismuth therapy. Gummatous tumours may still be palpable in such cases. To reduce the possibility of hepatic functional impairment to a minimum, the use of arsenic should be delayed. Thus I prefer to use bismuth and iodides for 8-10 weeks in such cases before giving arsenic. In the event of syphilitic disease in a cirrhotic liver having decreased hepatic function, it is wise to use only courses of bismuth alternating with rest periods.

In tertiary syphilis of a hollow viscus, it also seems best to use bismuth and iodides over a prolonged period of time in the hope of obtaining resolution with a minimum of scarring deformity. This might best be obtained by permitting almost complete healing of the lesion before arsenic therapy is introduced, namely, by the use of 8-10 weeks of bismuth and iodides.

Syphilitic iritis does not respond to bismuth therapy. Most therapeutists begin the use of arsenic at once. This may be justified on the

grounds that the need for symptomatic relief outweighs the chance of a Herxheimer reaction in some vital tissue. Iritis (iridocyclitis) of late syphilis, as in early syphilis, must also have the benefit of local treatment by the attending physician or, if possible, by an ophthalmologist. The local use of atropine either to prevent or to break up adhesions of the iris to the anterior lens capsule is imperative. Worthy of emphasis is the fact that iritis may be resistant to treatment with certain arsenical preparations, and not with others (Case 76). On several occasions we have seen that the use of either neoarsphenamine or mapharsen in adequate dosage was unsuccessful in relieving syphilitic iritis. A change to arsphenamine in these cases has been associated with very prompt involution of the process. It is also true that the iritis of late syphilis may relapse during the first bismuth course following the first arsenic course.

### PROGNOSIS AND RESULTS OF TREATMENT IN TERTIARY SYPHILIS

The untreated manifestations of late benign syphilis may undergo spontaneous involution. However, before it does so, it usually progresses for long periods—even for years—with extensive tissue destruction and consequent deformities and loss of function. Ocular syphilis, for example, may progress so that great impairment of vision or blindness results. Thus though untreated, late benign syphilis rarely leads to death, but it may cause invalidism and permanent changes which interfere with a normal productive life.

The healing of lesions is to be expected under treatment. Relapse may occur due to inadequate treatment. Wassermann and Goodman found that the chance of relapse in a patient who has had only one course or less of arsenic and some bismuth is almost seven times that in a patient who has had four or more courses of arsenic. In their cases 80 per cent of relapses occurred within six years after treatment was stopped. Commonly relapse occurred in the same tissues as the previous tertiary lesion. There is no good reason to believe that the tendency for relapse is greater in those patients who remain "Wassermann fast" than in those in whom reversal takes place under treatment. In fact, the above authors found more relapses in those patients who had become seronegative, but the difference is too small to be of statistical significance.

In the diagnosis of the various tertiary lesions it has been pointed out that practically all patients suffering with late benign syphilis present a positive blood test for syphilis. Treatment in a great many cases is followed by persistently positive tests of "Wassermann fastness." Therefore the practitioner should undertake the treatment of such disease with the expectation of a persistently positive serology, and with the realization

that treatment must be discontinued sooner or later in spite of this. Both he and the patient must be prepared for this, so that the patient will not be disappointed in the result. Spontaneous seroreversal may take place subsequently (Cases 73 and 75).

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## XI

# CARDIOVASCULAR SYPHILIS

## HISTORICAL NOTE

TRAUMATIC aneurysms of peripheral arteries were described by Galen in the second century. In the seventh century Aetius described rupture of arteries in the neck without external injury.

However, the first account of aneurysm of large internal arteries appeared in 1542 by Fernel. Pare in the sixteenth century wrote 'The aneurysmes which happen in the internal parts are incurable. Such as frequently happen to those who have often had the unction and sweat for the cure of the French disease because the blood being so attenuated and heated therewith that it cannot be contained in the receptacles of the Artery, it distends it to that largeness as to hold a man's Fist' ('Classic Descriptions of Disease'—Major).

In 1725 Morgagni found at autopsy, in a young woman who died during sexual intercourse, changes in the aorta in addition to a ruptured aneurysm. He wrote as follows: 'That is to say, in some places whitish marks of a future ossification occurred, and in still other places were paralleled furrows, drawn longitudinally, and in this manner was the surface of the artery unequal here and there' ('Classic Descriptions of Disease'—Major).

Corvisart in 1806 described symptoms and signs which may occur in aortic aneurysm. In 1833 Beron and in 1859 Flint added more information regarding clinical manifestations of aneurysm. Thoma in 1888 wrote concerning the pathology of aneurysmal formation.

In 1895 Dohle described the microscopic changes in syphilitic aortitis. Reuter in 1906 found the treponema in the wall of the aorta in cases of aortitis the year after Schaudinn and Hoffmann described the *T. pallidum*.

The previous chapters on clinical syphilis have dealt with manifestations of the disease but rarely attended by fatal outcome. In this and the following chapter the discussion will deal with late manifestations of syphilis which, if not always fatal, at least have an associated high morbidity rate.

## DEFINITION

In using the term cardiovascular syphilis we usually think, and correctly, of disease of the aorta with the secondary changes in the heart due to complications of the aortic disease. The use of such a concept is practical. Certainly for ordinary purposes we might limit our discussion to this, the dominant form of cardiovascular disease. However, for the sake of completeness, I feel that space, though brief, must be given to syphilis as it may affect the heart itself.

## SYPHILITIC MYOCARDITIS

Myocarditis in a diffuse form, as either a clinical or pathologic entity, has been believed to occur with extreme rarity, if at all. Only Warthin believed it to be relatively common, and demonstrated, to his own satisfaction, *T. pallidum* in the myocardium in thirty-six of forty-one instances in which he searched for them (See Chapter ix.) Associated with this he noted a pathologic lesion consisting of accumulations of lymphocytes and plasma cells in the myocardium (Other pathologists have pointed out that such cellular collections are not pathognomonic of syphilis.) The basic pathology of syphilitic myocarditis is an endarteritis of the small radicles of the coronary system, perivascular collections of round cells, and finally diffuse myocardial fibrosis. The fibrosis which Warthin thought to be the residuum of syphilitic myocarditis cannot be differentiated microscopically from that due to common infectious diseases, such as rheumatic fever and streptococcal disease (Scarring in the myocardium may occur in the presence of syphilis due to an impaired blood supply, as in those instances of aortitis in which the coronary orifices are partially obstructed.)

The fact that occasional localized gummatous myocarditis occurs cannot be denied. A fair number of such instances, proved at necropsy, have been reported. Gummata may be microscopic or may attain the size of a centimeter or more in diameter (The pathology of the gumma was discussed in the last chapter.)

## DIFFUSE SYPHILITIC MYOCARDITIS

Diffuse syphilitic myocarditis merely gives a clinical picture of impaired function of the myocardium without signs of valvular or other disease to account for it. Symptomatically, "heart consciousness," palpitation, dyspnea especially on exertion, and precordial discomfort may constitute the symptom complex. Frank failure may occur. At most the physical examination will reveal cardiac enlargement, tachycardia, and possibly premature contractions. The signs of cardiac failure, of the left or right ventricle, may be present. The roentgenogram may show cardiac enlargement. Electrocardiographic studies may show variable conduction disturbances. Every clinician immediately recognizes that such a collection of symptoms and signs proves nothing insofar as any specific etiology is concerned. The diagnosis of syphilitic myocarditis on such a clinical picture might be entertained merely on the basis of the exclusion of other more probable causes. In a syphilitic patient in the third or fourth decade of life, with such a syndrome and lacking any demonstrable cause such as hypertension, thyrotoxicosis, valvular heart disease, diphtheria, or other

recent infection, the question may arise, might syphilis be the etiologic factor? I doubt if the question could ever be answered with certainty. Case 78 is an example in point.

**Case 78** A twenty-eight year-old Negress complained of nervousness, palpitation, choking sensation, and attacks of rapidity of heart rate coming on suddenly but disappearing slowly. The onset of symptoms was six weeks before. She had genital lesions and enlarged lymph nodes about eight years before.

Physical examination was negative except for frequent extrasystoles. Roentgenogram showed slight enlargement of the left ventricle. The basal metabolic rate was normal. Blood Wassermann and Kahn tests were positive. Several electrocardiograms showed left-axis deviation, second-degree heart block with dropped beats, nodal, auricular, and at times ventricular extrasystoles.

The electrocardiographic changes and subjective symptoms disappeared during an eight week course of bismuth and iodides. Neoarsphenamine was then used, at first in small doses. Continuous treatment of alternating arsenic and bismuth was given for two years. Eight months after cessation of treatment, or thirty two months after the first admission to the clinic, the patient developed paroxysmal dyspnea and attacks of anginal pain. The electrocardiogram showed left axis deviation, the roentgenogram cardiac enlargement. She received two courses of bismuth and iodides without relief of symptoms.

**Comment** In this case there was evidence of myocardial disease which improved under antisyphilitic treatment. Did this represent syphilitic myocarditis? If so, did the subsequent development of angina pectoris and paroxysmal dyspnea represent the results of myocardial fibrosis, a therapeutic paradox?

In the differential diagnosis, in a fairly young person with the above clinical picture and syphilis of some years' duration, the other conditions to be considered are few. One is myocarditis caused by some acute infection, as rheumatic, streptococcal, diphtheritic, or the like. Another is the myocardial change associated with deficiency of thiamin. The difficulty in diagnosis was well illustrated in the only case reaching the necropsy table at Vanderbilt University Hospital in which the pathologist made a diagnosis of syphilitic myocarditis. In this instance, upon each of several admissions to the medical wards, a different diagnosis was made in an attempt to explain his myocardial failure. Syphilitic myocarditis was diagnosed clinically once. For practical purposes, I believe that the average practitioner may dismiss diffuse syphilitic myocarditis from mind.

#### LOCALIZED MYOCARDITIS (GUMMA OF THE MYOCARDIUM)

Here we are on firm ground regarding the clinical picture and its explanation on pathologic findings. Gummata have been found at autopsy in the walls of the ventricles, and in the interventricular septum. Healing with scar may be followed by aneurysm of the ventricle.

The clinical picture of gumma of the interventricular septum is due to interruption of the atrioventricular conduction pathway. There may be persistent complete heart block, or recurring heart block characterized by the Adams-Stokes attacks—attacks of syncope due to temporary cardiac standstill coincident with the change from normal to idiopathic ventricular rhythm or vice versa. The only physical sign of importance is the demonstration of the bradycardia of complete block. This can be corroborated by the electrocardiogram (Case 79). Partial heart block due to gumma of the ventricular wall interfering with conduction in one of the ventricular bundles has been reported. Practically, this can be demonstrated only by the electrocardiogram.

**Case 79** A fifty year-old Negro entered Vanderbilt University Hospital because of progressive dyspnea and orthopnea of seven weeks' duration. Within the thirty six hours before admission there had been three attacks of syncope, associated with unconsciousness. Following an attack on the street he was arrested for drunkenness, though he had not been drinking. There was no history of syphilis.

Examination revealed a pulse rate which ranged between thirty to thirty six beats per minute. There was slight cardiac enlargement. Blood Wassermann and Kahn tests were positive. The electrocardiogram confirmed the clinical diagnosis of complete heart block. Roentgenogram confirmed cardiac enlargement.

On the eleventh hospital day the pulse dropped to seventeen per minute, he became cold and clammy, and suddenly died.

Necropsy revealed the major finding to be a gumma of the heart muscle involving the atrioventricular bundle and the right coronary artery. There was also syphilitic aortitis with constriction of the orifice of the right coronary artery.

**Comment** The patient had Adams Stokes attacks, characteristically associated with the change in cardiac rhythm, due to a gumma.

The diagnosis of complete heart block due to syphilis would need to exclude arteriosclerotic heart disease, which is the cause of this condition in the vast majority of instances. Only with complete heart block in a relatively young syphilitic patient would the practitioner be justified in considering seriously the diagnosis of gumma of the interventricular septum. The disease may be influenced by antisyphilitic treatment, but the resulting scar might just as effectively interfere with conduction.

## SYPHILITIC AORTITIS

The complications of syphilis of the aorta—namely, aortic insufficiency and aneurysm—are made manifest in most instances in the second and third decades of the infection. However, during the stage of clinical latency, constant pathologic changes are going on in the wall of the aorta.



The frequency of these changes in Warthin's series was shown in Chapter ix. If these changes are of sufficient degree and at the proper site, one or both of the complications may appear. However, complications do not appear in all instances. Many patients go to their death from other causes twenty and thirty years after acquiring syphilis, with uncomplicated active aortitis and no symptoms related to the disease.

#### PATHOLOGY

Invasion of the aortic wall by the *T. pallidum* probably occurs early in the course of syphilis. Occasionally rare examples of the complications of aortitis are seen within the first few years of the disease. Invasion of the aortic wall probably takes place via the lymphatics from the mediastinal lymph nodes and the perivascular lymphatics of the vasa vasorum. The ascending and transverse portions of the aortic arch are especially well supplied with lymphatics, probably accounting for the greater frequency with which these sections are involved.

Syphilitic disease of the aorta is less frequent in the descending portions of the thoracic aorta, and is relatively infrequent below the diaphragm. The inflammatory reaction appears about the vessels of the adventitia and extends into the media along the perivascular lymphatics of the vasa vasorum. The cellular exudate consists of lymphocytes and plasma cells. Early in the disease treponemata may be demonstrable. As the result of obliteration of the vasa vasorum by the endarteritic process, necrosis develops in the media, and fragmentation of elastic tissue takes place. Replacement is by scar tissue. The thickness of the aortic wall is therefore variable. The intima overlying the active inflammatory lesion of the media becomes hyalinized, and subsequently may become atheromatous.

**Gross Alterations** Due to these microscopic changes certain gross alterations manifest themselves. These are so characteristic as to be diagnostic when present. The intima shows longitudinal creases or striation. The thickened patches of intima overlying the active mesaortitis are bluish-gray in colour, and of some 5-10 mm in diameter. Subsequently, scars may replace these with depressed areas in which the aortic wall is thinner. The aorta is dilated and lengthened, due to loss of elasticity. The intimal patches may involve the orifice of a coronary artery, at times reducing its calibre more than 75 per cent. Since the root of the aorta is so likely to be involved, dilatation of the aortic ring may occur. This may cause separation of the valve leaflets, and in addition there is frequently a sagging of the valve commissures so that aortic insufficiency develops. The valves themselves may be involved by the syphilitic process resulting in thickening and rolling of the edges. These also are factors in the development of incompetency. A focal point of weakness in the aortic wall may

give way, permitting the formation of a saccular aneurysm. The adventitia of the aorta becomes thickened as the result of the syphilitic process. In Case 80, the aorta shows some of these pathologic changes.

**Case 80** A thirty four year-old Negro labourer entered the Medical Clinic on April 24, 1939, because of "rheumatism." No symptoms were referred to the cardiovascular system. He had had a penile lesion twelve years before, at which time he had received less than a year of antiluetic treatment.

Examination of the cardiovascular system was negative. The pulse was slow, B P 140/70, the heart was of normal size, and the aortic second sound was not accentuated. Blood Wassermann and Kahn tests were positive.

The arthritis subsided and through an oversight the patient was not referred to the Syphilis Clinic, though a diagnosis of *late latent syphilis* had been made.

On June 19, 1940, he was again admitted to the Medical Clinic because of paroxysmal nocturnal dyspnea of a month's duration.

Examination disclosed the heart to be enlarged. A blowing, early, diastolic murmur was heard at the aortic area, and along the left border of the sternum. B P was 150/50. Capillary and Corrigan pulses were present. Roentgenograms showed cardiac enlargement, but no aortic dilatation. The spinal fluid was negative, except for a positive Wassermann reaction in 1 cc. of fluid.

The patient received bismuth  $\times 8$ . Treatment was stopped because of rapid progression of cardiac failure in spite of digitalis, diuretics, and bed rest. He was admitted to the medical wards four times between this time (August, 1940) and June, 1941. He died on the fourth admission, thirteen months after his first cardiac symptoms, and twenty six months after the diagnosis of latent syphilis was made.

Necropsy revealed syphilitic aortitis and valvulitis (Fig. 65).

**Comment** *This patient had an active aortitis in late latency. The diagnosis of aortitis could not have been made on the first admission. Within one year there was free aortic regurgitation. Had treatment in latency been undertaken, would the patient have developed regurgitation as in Case 84, as a 'therapeutic paradox,' or would the patient's life have been saved? This represents an example of the rapidity with which failure and death may occur in syphilitic aortic insufficiency, and it is obvious that nothing can be expected from antisyphilitic treatment under such circumstances.*

## UNCOMPLICATED AORTITIS

### FREQUENCY

A search of the literature regarding the frequency of uncomplicated syphilitic aortitis quickly shows that no figures are available that are really worth while. Most of the figures on the frequency of the condition have been reported from large city or charity hospitals. The patients in such hospitals are drawn especially from the ranks of society in which syphilis is most prevalent. Therefore these reports give a false idea of the frequency of aortic disease. Even if the figures are restricted to necropsy



FIG. 65. Syphilitic aortitis (Case 80). This shows the classic dull gray, wrinkled, and puckered areas of intima above the aortic valve (a); the thickened, rolled edges of the aortic cusps (b); the lowered attachment of the commissures as related to the level of the coronary ostia, and their separation (c), the narrowed coronary ostium (d); the thickening of the endocardium on the interventricular septum (e). (Courtesy of the Department of Pathology.)

findings in syphilitic patients, the figures are questionable since they are weighted on the side of increased frequency because disease brought the patient to the hospital.

Some of the studies on the prevalence of uncomplicated aortitis are based on the clinical diagnosis of this condition in syphilitic patients. Because of the notorious inaccuracy of the clinical diagnosis of uncomplicated aortitis, incidence figures based on such a diagnosis are, to my mind, worthless. Another common fault with statistics on aortitis is that in many papers both the uncomplicated and complicated cases of aortitis are lumped together.

Based on a clinical diagnosis the frequency of uncomplicated syphilitic aortitis in the Co-operative Clinical Group study was 4.9 per cent of 6,253 patients with latent or late syphilis. (The use of the term "latent" in the Group report is misleading.) At Johns Hopkins Hospital Turner in a study of the incidence of various types of syphilitic lesions found that among 6,000 patients with late syphilis, 5.3 per cent were diagnosed as having uncomplicated aortitis. This diagnosis was also made on clinical grounds only. Since I believe the incidence based on the clinical diagnosis is worthless, I shall not report the frequency of this diagnosis in our clinic.

Of more interest may be the statistics on the frequency of uncomplicated aortitis as found at necropsy in syphilitic patients at Vanderbilt University Hospital. Among 167 cases above the age of 15 years in which there was evidence of syphilis—either on history, serologic tests, or necropsy findings—there were 33 (19.6 per cent) in which the pathologist found uncomplicated aortitis. The race and sex distribution follows.

TABLE XXIV

INCIDENCE OF UNCOMPLICATED AORTITIS IN SYPHILITIC PATIENTS  
COMING TO NECROPSY

<i>Race and Sex</i>	<i>Total Necropsy (167 Cases)</i>	<i>Uncomplicated Aortitis at Necropsy (33 Cases)</i>
White male . . .	44	7
White female . . .	12	2
Coloured male . . .	75	17
Coloured female . . .	36	7

It may be of interest to contrast the prevalence of uncomplicated aortitis in necropsy material from a selected racial group as from my medical service, which was limited to coloured males, at Charity Hospital (New Orleans). From among the deaths on this general medical service 279 necropsies were performed. Pathologic evidence of uncomplicated

aortitis was present in 11.4 per cent (This is much higher than one would find in a series of white patients)

### SYMPTOMATOLOGY

Uncomplicated syphilitic aortitis rarely produces symptoms. This is unfortunate, for the physician has no way of recognizing the possibility of aortic involvement in the uncomplicated stage, and therefore the diagnosis is usually based upon suspicion only. Substernal pain and paroxysmal dyspnea may be the symptoms of uncomplicated aortitis. If these are present, they can be explained only upon a localization of the syphilitic process about the orifice of one or both coronary arteries, resulting in a decreased blood supply to the myocardium. Pincoffs and Love found anginal pain in fifteen of twenty-one cases having stenosis of the coronary ostia.

No instance of coronary ostial stenosis was found in the thirty-three cases of uncomplicated aortitis included in our study at Vanderbilt University Hospital. Among the thirty-two cases on my Charity Hospital service there were three such instances. Keefer and Resnik found no instances of paroxysmal dyspnea in twenty-four cases of uncomplicated aortitis coming to necropsy. Cardiac failure is not a part of the picture of uncomplicated aortitis. Only in the presence of stenosis of coronary ostia with impaired circulation in the coronary bed might myocardial changes with impaired function occur. In summary, one may say that uncomplicated aortitis is an asymptomatic condition except for an occasional instance in which a coronary orifice is practically occluded. Then cardiac pain and paroxysmal dyspnea may occur.

### EXAMINATION

Only rarely is the aortic dilatation of such degree that suprasternal pulsation or a heaving pulsation of the upper areas of the anterior chest wall are visible. At times pulsation in the suprasternal notch is palpable, but in the middle-aged group and upward this may be due to arteriosclerosis and hypertension. The aortic dilatation is rarely such that one may accurately demonstrate a widening at the base of the heart by percussion. Auscultation as a means of diagnosis is also of little assistance. In a rather marked supra-avalvular dilatation, a systolic murmur may be present at the aortic area. Accentuation or an amphoric (tambour) quality of the aortic second sound has been emphasized as being of significance in diagnosis. Except in a young person such a change cannot be accepted as of value since, in the middle-aged patient and beyond, arteriosclerotic changes and hypertension can cause these findings equally as well.

The roentgenogram has been urged as a means of examination to assist

in the diagnosis of uncomplicated aortitis. Its use here is disappointing, however. In complicated aortitis it is of assistance, but in the uncomplicated state in which help is needed most it is of no practical aid. Occasionally the roentgenogram will reveal a dilated aorta with increased pulsation noted on fluoroscopic examination, as in Case 81. The slight degrees of dilatation so often reported by roentgenologists must be carefully scrutinized. The clinician of experience recognizes the factors influencing the measurements of the aortic arch. These have been set forth by Sussman, a well-known roentgenologist, as age of the patient, technic, position of the diaphragm, posture, and chest deformity. He concludes with the statement that "the roentgen-ray examination of the aorta may not prove particularly valuable in the early diagnosis of luetic aortitis."

**Case 81** A thirty-eight-year-old white married mechanic complained of weakness and vertigo. Five months before admission he had noted onset of weakness which forced him to stop work. He was found to have a positive blood test, and his physician gave him sixteen intramuscular and two intravenous injections. The patient admitted some slight staggering, paresthesias of the feet, occasional pains in the legs, impaired libido, and a loss of ten pounds in weight. His sister noted some personality changes and irritability. About sixteen years before he had gonorrhea, and shortly thereafter was found to have a positive blood test for which he received six months of treatment, partly intramuscular and partly intravenous. He was dismissed from treatment because of a negative blood test.

Examination showed the pupils to be of the Argyll Robertson type. The heart was not enlarged, and the blood pressure was normal. There were no murmurs. The aortic second sound was loud. The deep reflexes in the legs were absent, and the Romberg test was positive. Blood Wassermann and Kahn tests were positive. Spinal fluid examination showed increased globulin, cells 2 per cu mm, Wassermann test positive in 10, 0.5, and 0.2 cc, with a 5554321000 mastic curve. Roentgenogram of the heart showed dilatation of the ascending aorta with marked pulsation upon fluoroscopic examination (Fig 66).

**Comment** Here uncomplicated aortitis with a dilatation demonstrable by roentgen-ray study was accompanied by a loud aortic sound. The need for complete study of the patient is well illustrated in this case. The findings of aortitis at once precluded the contemplated use of fever therapy for the taboparesis.

The electrocardiogram offers no assistance in diagnosis, unless stenosis of the coronary orifices is present. Under such circumstances changes compatible with coronary disease may be present, but they are not specific for a syphilitic process.

**Serologic tests in cardiovascular syphilis** are associated with a higher percentage of negative reactions than in other late syphilitic disease. In

the thirty-three cases of uncomplicated aortitis found at necropsy at Vanderbilt University Hospital, 66 per cent had positive serologic tests for syphilis and two of the remainder were doubtful

#### DIAGNOSIS

As may be gathered from the above discussion, the diagnosis of uncomplicated aortitis is difficult. Only pain or paroxysmal dyspnea, in a young syphilitic, may suggest stenosis of the coronary ostia by a syphilitic plaque. Otherwise the diagnosis is not possible except for the occasional case in which the roentgenogram reveals a definitely dilated aorta, as was shown in Case 81. In the summary of our study on the diagnosis of uncomplicated syphilitic aortitis, we arrived at the following findings. One-half of the thirty-three cases of aortitis found among 167 cases of syphilis coming to necropsy had no symptoms of cardiovascular disease. In the other half there was pathologic evidence of other disease offering a better explanation for the clinical picture than did the uncomplicated aortitis. Furthermore, in thirty syphilitic patients without the pathologic changes of aortitis, the incidence of symptoms and signs commonly ascribed to uncomplicated aortitis was greater than in those showing the lesion. We concluded the paper with a statement as follows, "We believe, on the basis of our studies, that the clinical diagnosis of uncomplicated aortitis is, for practical purposes, impossible." Certainly, as the result of observing much of both syphilitic and nonsyphilitic cardiovascular disease among coloured as well as white patients in the past decade, I must admit that it is impossible for me to make the clinical diagnosis of uncomplicated aortitis.

#### PROGNOSIS

On the basis of the pathologic process in uncomplicated aortitis, it would seem that this is the only form of cardiovascular syphilis having a hopeful outlook. Since it is not known what the actual frequency of this lesion is in syphilitic patients, it is impossible to forecast what percentage of the cases will progress to develop the complications of aortic incompetency or aneurysm. The Co-operative Clinical Group gives figures on the prognosis in treated and untreated uncomplicated aortitis. Since these statistics were based on the *clinical* diagnosis of aortitis, they cannot be accepted as answering the question. The outlook of aortitis should be good under treatment, and it is with the hope of preventing the later manifestations of cardiovascular disease that we so strongly urge the treatment of the late latent syphilitic patient. Many a patient in the stage of late latency has aortitis (Cases 80 and 84). In this stage of aortitis, in the absence of coronary ostial involvement, the heart is not overburdened,

and therefore treatment is directed toward the prevention of the complications. If we visualize what takes place in the treatment of late benign syphilis, we can hope to attain a similar course in the inflammatory reaction in the aortic wall. Treatment should lead to an involution of the inflammatory process in the adventitia and media. Scarring will result, but one can only hope that it will be minimal, and be in sites that will not lead to a valvular deformity as occurred in Case 84. Actually the prognosis in uncomplicated aortitis depends upon the adequate treatment of early syphilis (probably the stage of original aortic invasion), and to treatment in the stage of latency in order to combat the aortic disease which must be present in a quarter or so of the cases in this stage.

## AORTIC INSUFFICIENCY

The morbid anatomy of this complication of syphilitic aortitis has been discussed earlier in the chapter. Because of the definite physical findings associated with this complication, we are on firm ground with respect to diagnosis and prognosis.

### INCIDENCE

Syphilis has been found to be a relatively common cause of heart disease in some groups of society. In some of the statistics to be quoted the term syphilitic heart disease as a cause of death is taken to mean aortic insufficiency or aortic aneurysm, since only the very rare case of uncomplicated aortitis might end in sudden death. Because aneurysm of the aorta is much less frequent than aortic insufficiency, the bulk of the cases spoken of as "syphilitic heart disease" in statistics on cardiac disease must refer to valvular disease.

In the discussion of uncomplicated aortitis, I stated that there were thirty-two instances of such a lesion in 279 necropsy cases, from my general medical service consisting only of adult Negro males at Charity Hospital. In this same group of necropsy cases there were found twenty-nine instances of aortic insufficiency. At first glance it may seem strange that there should be practically the same number of patients as had uncomplicated aortitis. A higher incidence of aortic regurgitation is to be expected since this disease forces the patient to enter the hospital.\*

The frequency rate of aortic insufficiency among syphilitic patients will vary a great deal with race, sex, age, amount of antisyphilitic treatment, and economic status. Among the 6,253 cases of late and "late latent" syphilis in the Co-operative Clinical Group study, the incidence was 4.1

\* It may be of interest to contrast the prevalence of syphilitic aortic insufficiency with that of rheumatic valvular disease which is less common in the South, and relatively rare of the Negro race. In the 279 necropsy cases there were seven instances of rheumatic valvular disease.



per cent, only slightly less than the number of cases of uncomplicated aortitis diagnosed as such clinically. Turner in 6,000 cases of late syphilis at Johns Hopkins Hospital found aortic insufficiency in 27 per cent. Among 2,961 cases of late syphilis in the Vanderbilt University Hospital Syphilis Clinic, there were ninety instances of aortic insufficiency, or an incidence of 3 per cent. Thirty-two cases were found among the 167 necropsies done on syphilitic patients over the age of fifteen years in this institution.

Race and sex seem to be prominent factors in the development of the complications of syphilitic aortitis. Most authors agree that the complications are more frequent in the Negro race than in the white race. It is granted that syphilis is more common in the coloured race, but the proportional frequency of complicated aortitis in this race is greater than the higher prevalence of the infection. Whether the increased incidence of aortic complications in the coloured race is due to a predilection to vascular disease or due to the higher incidence of heavy labour in the race is not known. It seems probable that the latter is a potent factor in the development of the complications of syphilitic aortitis. In the Co-operative Clinical Group studies the incidence of aortic insufficiency was 3.4 per cent in 5,089 white patients, and 7.2 per cent in 1,164 coloured patients. We carried out a study upon 163 cases of syphilitic aortic insufficiency at Vanderbilt University Hospital. The racial and sex incidence was as follows: Negro males 91, Negro females 37, white males 27, and white females 8.

#### SYMPTOMATOLOGY

(Cases 58, 80, and 84.) Some patients with aortic regurgitation are found in the asymptomatic state. They are usually cases in which the finding is a chance one on routine physical examination. Of the 163 cases at Vanderbilt University Hospital, twenty-five were detected during examination for other conditions. Usually the patient with aortic insufficiency presents himself because of early symptoms of cardiac failure. These symptoms present themselves most often in the third to fifth decade of life. Textbooks have placed too much stress upon the symptoms appearing in the fifth decade of life. The appearance of symptoms is related not to age, but to the duration of the syphilitic infection. In the majority of instances the symptoms and signs of aortic regurgitation appear in the second or third decade of the syphilitic infection. Thus in the Negro, whose sex life often begins at 13 to 15 years of age, it is not unusual to see the manifestations of aortic disease in the late twenties or early thirties. Rarely, advanced aortic disease may develop early. (Within recent years we have followed a patient in our clinic who developed

the murmur of aortic insufficiency and symptoms of myocardial embarrassment within twenty-two months of the secondary stage of infection in spite of fairly adequate treatment. An aneurysm also was present. The patient became progressively worse and died within 5 5 years after his infection was acquired.)

The presenting symptoms may be those of varying degrees of congestive failure, cardiac pain, and/or paroxysmal dyspnea. The symptoms of decreased myocardial reserve due to the burden of regurgitation of blood from the aorta may vary from slight dyspnea on exertion to frank congestive failure. In the latter instance there will be the signs of orthopnea, dyspnea, cyanosis, edema, fluid in the serous cavities, and moisture at the lung bases. Paroxysmal dyspnea ("cardiac asthma") is common and has a serious prognostic significance. There may be the pain of angina pectoris. It is probably related to either free regurgitation with an attendant poor coronary flow, or to stenotic coronary orifices caused by syphilitic plaques. (Five of my twenty-nine necropsy cases at Charity Hospital showed this latter type of lesion.) Table XXV indicates the frequency of the common symptoms in 163 patients with aortic insufficiency at the time of their initial visit at Vanderbilt University Hospital.

TABLE XXV

SYMPTOMS IN 163 PATIENTS WITH AORTIC INSUFFICIENCY

<i>Symptom</i>	<i>Number of Cases</i>	<i>Per Cent</i>
Chance finding (asymptomatic)	25	15
Dyspnea	120	74
Orthopnea	88	54
Paroxysmal dyspnea ("cardiac asthma")	64	39
Cough	73	45
Cardiac pain	67	41

## EXAMINATION

Only those signs related to the valve lesion will be reviewed. (The signs of advanced cardiac failure in syphilitic aortic regurgitation are no different from those due to the cardiac failure of other causes.) Inspection at the bedside may make the diagnosis promptly in the presence of free regurgitation if the nodding of the head with each heartbeat is noted. Pulsation of the carotid arteries may be prominent, and visible pulsation in the suprasternal notch is common.

The position of the apex beat of the heart depends upon the degree of cardiac enlargement which has occurred, and this in turn is related to the duration of the lesion and the degree of incompetency of the valve. Thus

the apex may be within normal limits or may be in the sixth intercostal space and in the midaxillary line. Palpation shows the position of the apex beat, and the heaving thrust of an enlarged left ventricle. Percussion will outline a great left ventricle in the advanced case, and often a widening at the base of the heart due to the dilated aorta.

Auscultation will reveal the presence of an early high-pitched blowing diastolic murmur in the second right intercostal space close to the sternum. Usually it also will be well heard in the third or fourth interspace to the left of the sternum. Transmission of the murmur is downward and to the left, and thus it may at times be heard even at the apex of the heart. Faint murmurs can often be brought out by listening at a time when the patient holds his breath in expiration, sits up, and leans forward. Early murmurs may be heard best at the third left interspace near the sternum. The aortic second sound may be variable in character, faint or accentuated depending upon the degree of regurgitation. A systolic murmur is commonly heard over the large vessels. The Austin-Flint murmur of functional "mitral stenosis" may be present in free regurgitation. The pulse is of the so-called Corrigan type, in which the pulse is quick and forceful but recedes at once. This can be brought out best by holding the wrist high above the patient's heart level. The capillary pulse is an attendant phenomenon, and can be seen as a to-and-fro flushing, with or without pressure, in the nail beds or in the mucous membranes. The presence or absence of these two findings is dependent upon the degree of insufficiency. The blood-pressure findings also are variable depending upon the degree of insufficiency. In free regurgitation the systolic pressure is usually high—150-200 mm. of mercury—because of increased cardiac output, and the diastolic pressure is low—under 50-60 mm. of mercury—thus giving the increased pulse pressure. Such changes will be much less marked in milder grades of incompetency. The frequency with which certain physical signs occurred in the 163 Vanderbilt University Hospital cases may be seen in Table XXVI.

The roentgenologic examination in cases of aortic insufficiency will reveal variable degrees of aortic dilatation. Aortic dilatation is, in general, a much more constant finding than in simple aortitis. (The roentgenogram will be similar to that seen in Fig. 66.) Upon fluoroscopic examination, increased pulsation of the aortic arch will be found. Hypertrophy of the left ventricle is obvious in the advanced case.

The electrocardiogram has no specific diagnostic value. Left ventricular preponderance and evidence of coronary disease may be demonstrated, but the changes may be no different from those in hypertensive heart disease.

Serologic tests, as in uncomplicated aortitis, are negative in a fair

TABLE XXVI

PHYSICAL SIGNS IN 163 PATIENTS WITH AORTIC INSUFFICIENCY

<i>Physical Signs</i>	<i>Number of Cases</i>	<i>Per Cent</i>
Aortic diastolic murmur	163	100
Austin-Flint murmur	26	15
Collapsing pulse	76	47
Systolic B P 140-159	25	15
Systolic B P 160 or over	81	50
Diastolic B P 60 or less	51	31
Congested cervical veins	39	24
Moisture lungs	61	37
Effusion into serous cavities	16	9
Hepatic congestion	73	45
Edema	77	47

proportion of cases Of 163 cases studied at Vanderbilt University Hospital, 85 per cent showed a positive blood test Of the remaining twenty-three cases, nineteen had collateral evidence of syphilis A positive spinal fluid may offer collateral information Among our cases, forty-five were subjected to spinal puncture, eleven of these had a positive Wassermann reaction in the spinal fluid The incidence of some degree of positive blood tests for syphilis in the Co-operative Clinical Group cases was also 85 per cent

## DIAGNOSIS

The diagnosis of syphilitic aortic insufficiency is on firm ground in contrast to that of uncomplicated aortitis Given a syphilitic patient with the murmur of aortic incompetency, a dilated aortic arch upon roentgenologic examination, and whatever attendant symptoms and signs there may be, there is usually no question of the diagnosis (Occasionally the landmarks of present or past late benign syphilis may assist in the diagnosis See Case 58) Occasionally, however, other forms of heart disease must be thought of in differential diagnosis

Rheumatic aortic insufficiency must at times be considered in diagnosis, but is uncommon without mitral disease However, the functional Austin-Flint murmur associated with syphilitic aortic insufficiency can mimic fairly closely the murmur of rheumatic mitral stenosis A rheumatic history, a negative blood test for syphilis, and in general the younger age of the patient will aid in making a diagnosis of rheumatic aortic insufficiency However, at times the diagnosis is not so easy The presence of cardiac pain almost certainly points to syphilitic disease The roentgenologic demonstration of a dilated aorta is indicative of syphilis Rarely,

in association with mitral stenosis, accompanied by marked congestion in the pulmonary circulation, a murmur of relative pulmonary insufficiency (the so-called Graham Steele murmur) may be heard. This is a faint early diastolic murmur at the left of the sternum, and may suggest the murmur of aortic insufficiency. Finally, we have seen rheumatic heart disease in the patient with latent syphilis.

Hypertension of high degree and of prolonged duration may rarely be accompanied by a relative aortic regurgitation due to slight dilatation of the aortic ring. This condition generally offers no difficulty in diagnosis. A history of longstanding hypertension may be elicited, the systolic blood pressure is usually 250 mm. of mercury or more, and the regurgitation is not free enough to produce the signs of an ill sustained intra aortic pressure, as shown by the absence of a collapsing pulse and low diastolic pressure.

Arteriosclerosis with calcification of the aortic valves occurs in the very aged. Because of deformity of the aortic valve cusps a regurgitation may occur. This is not likely to be free, and is prone to be associated with a harsh systolic murmur and a systolic thrill.

#### PROGNOSIS

The ultimate prognosis in syphilitic aortic insufficiency depends upon the state of the myocardium. This in turn is dependent upon the degree of valvular incompetency, the age of the patient, the type of physical work, and the presence or absence of chronic myocardial changes due to impairment of the blood flow in the coronary bed. The factors which might interfere with blood flow are coronary arteriosclerosis, syphilitic obstruction of the orifices of the coronary arteries, and such free regurgitation that not sufficient intra aortic pressure during diastole is maintained to allow of sufficient flow into the coronary system. It seems as if these factors will be the chief ones operating in the determination of the ultimate outcome.

The Co-operative Clinical Group in an analysis of their 260 cases found that the average duration of life was increased from forty months to fifty-five months by the giving of adequate antisymphilitic treatment after the diagnosis of syphilitic aortic insufficiency had been made.

We analysed 163 cases of syphilitic aortic insufficiency that had been followed at Vanderbilt University Hospital. Seventy-three of the patients had died, 54.6 per cent of the deaths had occurred within three years of the onset of symptoms. Race and sex (to which heavy labour is obviously related) seemed to be of great importance in the prognosis of syphilitic aortic regurgitation. Only a fourth of the Negro males lived three or more years after the appearance of symptoms, whereas slightly less than a half

of the white males and Negro females and over one half of the white females lived three or more years

Symptomatology was an important factor in the prognosis in our cases. Of the 163 cases, aortic insufficiency was a chance finding in twenty five instances, distributed as follows

- 2 were among 89 patients dying within 3 years after diagnosis
- 6 were among 31 patients dying after 3 years after diagnosis
- 9 were among 18 patients alive at 36 months after diagnosis
- 8 were among 25 patients alive for 37-168 months after diagnosis

In the symptomatic cases an evaluation of the state of the myocardium as found upon the first admission was made on the basis of exertional dyspnea, orthopnea, paroxysmal dyspnea, and cough. These symptoms were twice as frequent among the patients dying within three years of the time of diagnosis as among those still alive at the time of the study. In those dying subsequent to the first three years from the time of diagnosis, these symptoms were one half as frequent as those dying within three years. Congestive failure upon the first examination was twice as frequent in cases dying in less than three years as in those living beyond this period. The signs of failure were several times more frequent in patients dying within three years than in those alive at the time of the study. If the collapsing pulse, the Austin-Flint murmur, and a diastolic pressure of less than 60 mm of mercury are taken as evidence of free regurgitation, it was found that these were two or three times more common in those patients who succumbed than in those living at the time the study was completed.

Our findings appear to bear out Padget and Moore's beliefs in that adequate treatment after the diagnosis of valvular disease seemed of value since the duration of life of the inadequately treated patients was 36.2 months as against 60.3 months for adequately treated cases. But a preponderance of males contributed to the inadequately treated group. Actually, inadequately treated females lived as long as adequately treated males. Inadequately treated white males lived 40 per cent longer than inadequately treated coloured males. Though the following point will prove nothing until the death of these patients, it is of interest nevertheless. Of the thirty-nine patients alive at the end of the study, all having lived more than one year from the onset of symptoms, seventeen inadequately treated cases had lived an average of 80.6 months and twenty two adequately treated cases an average of 60.3 months.

We could not conclude that antisymphilitic treatment altered the outlook in syphilitic aortic insufficiency, but rather that the prognostic factors considered above were of more importance. One wonders, in those cases

in which life was of greater duration, whether such was the result of treatment or whether they received "adequate" treatment because they lived longer!

## ANEURYSM OF THE AORTA

In the general discussion of the pathology of syphilitic aortitis it was shown how, through weakening of the media and adventitia by inflammation and scarring, either diffuse dilatation of the aorta may occur, or a localized weakened area may permit an outpouching and development of a saccular aneurysm. The fact that the latter represents a localized weakening is demonstrated by the definite ring which outlines the mouth of the aneurysmal sac in most instances. Though the sac may vary in size from a walnut to a large grapefruit or even greater, the opening of the sac is often no larger than a sixpence to a crown in size.

### DEFINITION

True aneurysms are those in which one or more of the coats of the vessel form the wall of the tumour. For practical purposes all aneurysms of the aorta are syphilitic except the dissecting form which is due to arteriosclerosis. The term "dilatation aneurysm" is applied to a rather marked diffuse dilatation of the aortic arch as is often seen in aortic insufficiency—this may be cylindrical, or if more marked at some segment of the arch, may be spoken of as fusiform. Dilatation of the whole aorta, even involving the larger vessels arising from it, is spoken of as cirroid aneurysm. The common aneurysm which constitutes a clinical entity is the saccular one which presents a tumour arising from the aorta and filled partially or entirely with blood, or partially filled with a firm laminated fibrin and blood clot of varying thickness. Calcification of such a clot may occur in rare instances and under such circumstances "healing" is said to have occurred.

### ANEURYSM OF THE THORACIC AORTA

**Incidence.** This will vary greatly with the material used for study. The frequency will be highest in analyses of admissions to the large charity hospitals and among the coloured race. The clinical diagnosis of aortic aneurysm, as published in hospital statistics from various parts of the world, has varied from 1 per 105 to 1 per 1,359 patients. In necropsy statistics, also from various parts of the world, aneurysm has been found in 1 per 34, to 1 per 331 necropsies, the latter being the incidence at Vanderbilt University Hospital. Among 6,253 patients in a late stage of syphilis studied by the Co-operative Clinical Group, there were 73 instances of aneurysm, an incidence of 1.2 per cent. Thirty-seven of these were found

among 5,089 white patients, and 36 instances among 1,164 coloured patients. At the Vanderbilt University Hospital Syphilis Clinic there have been 38 cases of aortic aneurysm (exclusive of those treated on the wards and who have never been patients in the Syphilis Clinic) among 2,961 patients with late syphilis—a frequency of 1·2 per cent.

In a series of 633 cases of saccular aneurysm I collected from Charity Hospital at New Orleans and Vanderbilt University Hospital, it was found that the ratio of aneurysms in white patients to Negroes was 1·3·1. The admission ratio of the races was 1·3·1 in Charity Hospital. With regard to sex, the distribution was as follows: in Negro males 279 (59·8 per cent), white males 131 (20·8 per cent), Negro females 103 (16·1 per cent), and white females 18 (2·8 per cent). The ratio of cases of aortic aneurysm in the coloured race was, male to female, 2·7·1, and 7·9·1 in the white race, or an average of 5·8 males to 1 female. The relationship of heavy labour to aortic aneurysm was indicated to be quite definite in this study, since the disease was found predominantly in persons who had done manual labour.

As in the case of aortic insufficiency, age is of importance probably only as related to the duration of the syphilitic infection. The earlier age of infection in the coloured race is shown by the fact that the highest incidence of aneurysm for both sexes occurred in the 36- to 45-year-old group. Among the white patients, the highest incidence for males occurred in the decade forty-six to fifty-five years, whereas among females one-third fell into each of the decades forty-six to fifty-five years and fifty-six to sixty-five years. Six cases of aortic aneurysm were found in Negroes between the ages of twenty to twenty-five years.

**Symptomatology and Signs** If symptoms or signs make themselves manifest in the patient having a saccular aneurysm of the thoracic aorta, they do so in most instances between ten and thirty years after the acquisition of syphilis. In my series of 633 cases, 242 patients gave a history of a presumed acute stage of syphilis. Of these 113 gave the date of infection as from eleven to twenty years before. (Obviously these figures are not accurate since some of the genital lesions may have been nonsyphilitic.) The duration of symptoms in 596 cases of thoracic aneurysm at the time of admission to the hospital in my series was from a few days to ten to fifteen years. Most cases had had symptoms of from two to twelve months.

As will become evident below, the symptoms and signs of saccular aneurysm are related very closely to the anatomic point of origin of the sac from the thoracic aorta, and the direction in which it points. It has been the general custom to speak of sacs arising from the ascending arch, the transverse arch, the descending arch, and of the descending thoracic aorta. The ascending arch is that segment of the arch between the



valve and the origin of the innominate artery, and lies fairly close to the anterior chest wall. The second portion of the arch lies transversely in the mediastinum, and is intimately related to the esophagus, trachea, left bronchus, and left recurrent laryngeal nerve. The descending arch is that part of the arch lying to the left of the third to sixth dorsal vertebrae, adjacent to the esophagus and left bronchus. The descending thoracic aorta extends from the sixth dorsal vertebra to the diaphragm.

The symptomatology and signs in saccular aneurysms of the thoracic aorta are dependent entirely upon the fact that the expanding tumour presses upon some structure. The anatomic structure thus involved determines to a large degree the clinical picture and may give rise to very interesting diagnostic problems. Structures or organs which may be pressed upon are the trachea, major bronchi, lungs, esophagus, pulmonary artery, vagus and sympathetic nerves, right laryngeal and left recurrent laryngeal nerves, intercostal nerves, rarely the diaphragm, and indirectly the stomach. Pressure erosion of bones, as ribs and sternum, with a protruding pulsating tumour is common. Erosion of vertebrae may lead to bizarre neurologic syndromes because of pressure upon the spinal cord or the segmental nerves.

If the clinician will keep in mind the relationship of the aorta to the various intrathoracic organs, the symptomatology and signs generally will be clear. A sac of the ascending arch tends to point upward, forward, and to the right, and is spoken of as the "aneurysm of signs," that arising from the transverse arch is called "aneurysm of symptoms." Aneurysms of the descending portion of the aortic arch are less common, and are rare in the lower thoracic portion. In the latter site aneurysmal sacs are often "silent," giving rise to neither symptoms nor signs even though they may be the size of a large grapefruit. Aneurysms at this site give the clinician his greatest surprises when he is confronted by postmortem or roentgenologic evidence of such an unsuspected tumour. More than one aneurysmal sac occurred in twenty-five of the 596 cases. Under such circumstances mixed clinical pictures may appear.

With this general background of the production of symptoms and signs, Tables XXVII and XXVIII are indicative of the clinical possibilities in aneurysm of the thoracic aorta. Only imagination limits the possible combinations. These tables were taken from my study of 633 cases of aortic aneurysm. (In the original report some of these tables are further amplified.)

(In relatively few cases is there an accompanying aortic regurgitation which may cause the picture of cardiac failure.) There were examples of reference of pain to every portion of the chest and back as well as to head, face, shoulders, arms, epigastrium, and abdomen in general.

TABLE XXVII

SYMPTOMS OF THORACIC AORTIC ANEURYSM AS RELATED TO THE SITE OF THE SAC<sup>1</sup>

<i>Symptoms</i>	<i>Ascending Arch (214 Cases)</i>	<i>Transverse Arch (205 Cases)</i>	<i>Descending Arch (147 Cases)</i>	<i>Descending Thoracic (30 Cases)</i>
Pain . . . . .	132	123	106	26
Dyspnea . . . . .	140	131	76	10
Cough . . . . .	117	119	75	9
Palpitation . . . . .	32	18	11	3
Hoarseness . . . . .	34	63	36	2
Dysphagia . . . . .	16	40	12	2
Hemoptysis . . . . .	18	17	19	3
Tumour . . . . .	37	32	10	2
Edema of legs . . . . .	43	24	14	1
"Choking spells" . . . . .	2	15	2	—
Vertigo . . . . .	17	20	7	—
Sputum . . . . .	42	45	26	5
No history obtainable . . . . .	9	7	8	1

<sup>1</sup> From Ann. Int. Med.

A detailed table in the original paper records the frequency of signs of pressure due to aneurysmal sacs of the thoracic aorta. These include cyanosis and edema of the face, and dilated veins of the upper chest and shoulders. Deviation of the trachea, respiratory stridor, and demonstration of esophageal pressure by use of the barium meal—all are important evidences of pressure on vital structures. Pupillary changes register pressure on the sympathetic chains. Vocal-cord paralyses are due to pressure on one or other laryngeal nerve. Inequality and asynchronicity of radial pulses and differences of the blood pressure in the two arms signify pressure on vessels arising from the arch. Various neurologic findings may occur due to pressure on the spinal cord or its roots. Cases 82 and 83 have been chosen to illustrate some of the symptoms, signs, and evidences of pressure which may occur in aneurysm of the thoracic aorta.

**Case 82.** A fifty-five-year-old Negro was admitted to the author's Medical Service at Charity Hospital because of dyspnea of eight months' duration, and edema of the feet. In the two weeks before admission he noted pain in the right chest, marked dyspnea, cough with much sputum which was blood-streaked at times.

Examination disclosed pulsation, and fullness was noted in the third and fourth interspaces of the right front of the chest. The percussion note was dull, breath sounds were tubular, somewhat stridulous, and large rales were

TABLE XXVIII

PHYSICAL SIGNS OF THORACIC AORTIC ANEURYSM AS RELATED TO THE SITE OF THE SAC<sup>1</sup>

<i>Physical Signs</i>	<i>Ascending Arch</i> (214 Cases)	<i>Transverse Arch</i> (205 Cases)	<i>Descending Arch</i> (147 Cases)	<i>Descending Thoracic Arch</i> (30 Cases)
Tracheal tug . . . . .	14	22	7	1
Thrill . . . . .	38	22	19	2
Diastolic shock . . . . .	10	11	10	1
Pulsation, suprasternal . . . . .	8	21	6	1
upper chest . . . . .	—	4	—	—
right upper chest . . . . .	33	—	—	—
left upper chest . . . . .	—	9	14	1
supraclavicular . . . . .	4	—	—	—
neck . . . . .	2	6	2	—
left interscapular . . . . .	—	—	17	1
Retrosternal dullness . . . . .	45	62	9	—
Dullness right of sternum . . . . .	26	—	—	—
Cardiac enlargement . . . . .	79	64	38	—
Systolic murmur at apex . . . . .	96	64	60	11
at base . . . . .	59	35	21	4
Diastolic murmur at base . . . . .	54	33	26	4
Aortic second accentuated . . . . .	25	38	26	1
Signs of cardiac failure . . . . .	30	21	11	1
Fever . . . . .	42	49	37	7

<sup>1</sup> From Ann. Int. Med.

heard over the right chest. The front of the chest and abdomen revealed a most remarkable venous pattern. Many veins traversed the trunk in a longitudinal direction, and some of these over the abdomen were of the diameter of a lead pencil. Blood tests for syphilis were positive. Roentgenogram revealed a large aneurysm of the ascending arch. Intratracheal injection of lipiodol showed bronchial compression with the bronchi of the middle lobe sweeping around the sac in a semicircle. The patient died two months after admission.

At necropsy it was found that the aneurysmal sac compressed the right upper and middle lobes of the right lung. The sac arose from the ascending arch, the ring of the opening was 3 cm. in diameter. The sac was 11 cm. in diameter, and was partially filled with a laminated clot. It compressed the right main bronchus and there was some degree of bronchiectasis. The mucosa of the esophagus, at an area pressed upon by the sac, showed an ulcer 3 cm. in diameter.

**Comment.** In this instance it is shown that an aneurysmal sac may cause

TABLE XXXI

SCHEDULE FOR TREATMENT OF UNCOMPLICATED AORTITIS<sup>1</sup>

<i>Time (in weeks)</i>			<i>Drug</i>
10	.	.	Bismuth in oil, weekly
8	.	.	Neoarsphenamine, or arsenoxide, weekly
10	.	.	Bismuth in oil, weekly
8	.	.	Neoarsphenamine, or arsenoxide, weekly
10	.	.	Bismuth in oil, weekly
8	.	.	Neoarsphenamine, or arsenoxide, weekly
12	.	.	Bismuth in oil, weekly
8	.	.	Neoarsphenamine, or arsenoxide, weekly
12	.	.	Bismuth in oil, weekly
12	.	.	Rest
12	.	.	Bismuth in oil, weekly
12	.	.	Rest
12	.	.	Bismuth in oil, weekly
Total 134 weeks			Total Arsenic—32      Bismuth—78

<sup>1</sup> For dosage, see preceding paragraph.

finding upon physical examination, and in which no symptoms of decreased myocardial reserve have ever been present, the same scheme of treatment may be carried out as outlined for the case of uncomplicated aortitis.

However, few patients are found in the asymptomatic stage of aortic insufficiency. The great majority will either have some evidence of decreased myocardial reserve, have had congestive failure, or be in frank congestive failure. If failure is present, all antisyphilitic treatment is interdicted. Only the drugs necessary for the management of cardiac failure should be used. Some patients who remain in "chronic" failure will therefore never receive any antisyphilitic treatment. It is obvious that the bedridden cardiac patient, or one confined to a chair with orthopnea, edema, etc., *should not be punished by antisyphilitic treatment. Such a patient should be permitted to rest in peace during the remaining weeks or months of his life.*

If some fair degree of myocardial reserve has been re-established and the patient is ambulant and comfortable, it is our opinion that the following conservative plan of treatment is sufficient. In view of the condition under which many of the readers will have to treat syphilis, I believe it wholly justified. Less harm is done in cases of aortic regurgitation with some impairment of myocardial reserve by interdicting the use of arsenic entirely, than by the injudicious use of this drug.

Therefore in this group of cases *only heavy metal should be used.* The patient should receive bismuth salicylate for four to six months by

weekly injections. If bismuth pigmentation of the mucous membranes occurs, a change may be made to mercury inunctions for six to eight weeks, and then bismuth should again be used. If gingivitis is present a rest from treatment may need to be given rather than mercury inunctions. Iodides should be used for eight to twelve weeks at the beginning of treatment, and at intervals subsequently. Alternating periods of rest with courses of bismuth and iodides are continued for two to three years, somewhat as in Table XXXII.

TABLE XXXII

SCHEDULE FOR TREATMENT OF COMPLICATED AORTITIS (AORTIC INSUFFICIENCY AND ANEURYSM)

<i>Time (in Weeks)</i>	<i>Drug</i>
36 .	Bismuth in oil, weekly or daily mercury inunctions for a part of this period (see above)
8	Rest
12	Bismuth in oil, weekly
8	Rest
12 .	Bismuth in oil, weekly
12	Rest
12	Bismuth in oil, weekly
12	Rest
12	Bismuth in oil, weekly
Total 124 weeks	Total Bismuth—84 (Some of the bismuth may need to be replaced by mercury inunctions)

It is my feeling that the general practitioner or health officer should treat aortic aneurysm in the same fashion as that outlined for aortic insufficiency in the patient with decreased myocardial reserve. Certainly the attending physician will not get into difficulties by following some such plan.

#### PROPHYLAXIS

From the above discussion of treatment it is apparent that at best the effect of treatment in complicated aortitis is to be measured only in possible prolongation of life. Therefore this is a proper time to point out that the advantageous time to treat cardiovascular syphilis is before it develops. This in simple terms means the adequate therapy of early and latent syphilis.

Moore states that of 2,889 early syphilitic patients treated in the clinics of the Co-operative Clinical Group, only thirty of those treated with varying amounts of arsphenamine had developed cardiovascular syphilis at the time of the study. Of course it must be noted that the time within which the greater number of cases of cardiovascular disease develop had

not been reached in this study. In his Johns Hopkins Hospital material, Moore found that no patients who had received twenty-four injections of arsenic had developed aortitis, whereas 9 per cent of those treated with less had developed uncomplicated or complicated aortitis. This figure is approximately the same as that in Bruusgaard's untreated series. Of the 163 cases of aortic insufficiency studied at Vanderbilt University Hospital, only fourteen patients had received adequate treatment in the past.

Whether the figures from Charity Hospital as shown in the following table indicate more and better treatment of syphilis in recent years I do not know. It is of interest, however, to note that there is a decreasing proportion of aortic aneurysms to hospital admissions. (The ratio of admissions as between white and coloured races has not changed appreciably.)

TABLE XXXIII

INCIDENCE OF AORTIC ANEURYSM IN FIVE YEAR PERIODS AS RELATED TO HOSPITAL ADMISSIONS (CHARITY HOSPITAL)<sup>1</sup>

Years	Accepted Cases of Aneurysms	Hospital Admissions	Ratio of Aneurysms to Admissions
1906-1910, inclusive	42	47,736	1 1136
1911-1915, inclusive	79	74,117	1 925
1916-1920, inclusive	91	90,613	1 995
1921-1925, inclusive	109	105,330	1 966
1926-1930, inclusive	136	166,086	1 1221
1931-1935, inclusive	134	282,480	1 2854

<sup>1</sup> From Ann. Int. Med.

The proper treatment of the patient with early syphilis or latent syphilis will reduce the subsequent development of aortitis and its complications to a minimum.

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## XII

# SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

## HISTORICAL NOTE

ACCORDING to Pusey, gumma of the cerebrum and syphilitic meningitis were described in the sixteenth century. In 1822, Bayle expressed the belief that general paralysis with mental disease was due to chronic meningitis. Several years later Calmeil showed that it was really an encephalitis, since both brain and meninges were involved. It was recognized that many persons suffering from general paralysis had had syphilis. In 1856 Gull described the posterior column lesions of tabes dorsalis. During the last decade of the nineteenth century Fournier spoke of locomotor ataxia and general paresis as related to syphilis, and applied the term "para syphilis." At about this time Krafft-Ebing inoculated infectious syphilitic material into parietic patients without the production of a chancre, which suggested the presence of syphilis in such patients.

With the demonstration of positive Wassermann tests on the spinal fluid, early in the present century, the relationship of syphilis to general paresis seemed to be established. In 1913 Noguchi and Moore reported the demonstration of *T. pallidum* in the cerebral cortex of fourteen out of seventy patients who had general paresis.

## TIME OF INVASION BY *T. PALLIDUM*

It is probable that the central nervous system commonly is invaded by the *T. pallidum* early in the course of the infection. Various investigators have found some change in the spinal fluid (usually merely a pleocytosis and an increase in globulin) in 33 per cent or more of cases in the late primary or early secondary stage of syphilis. Furthermore, it has been shown that the apparently normal spinal fluid may contain treponemata. Chesney and Kemp, in a study of the infectiousness of spinal fluid in early syphilis, inoculated 0.75-3.0 cc. of uncentrifuged fluid into rabbits. (No fluid showed a greater abnormality than 9 cells per cu. mm.) Positive inoculation results were obtained in 14 per cent of the fluids. In similar studies collected from the literature they found that from 14.7 to 26.6 per cent of apparently normal spinal fluids in early syphilis contain *T. pallida*.

The Co-operative Clinical Group found evidence of abnormal spinal fluids in the acute stages of syphilis as follows: in the seronegative primary 25 per cent, in the seropositive primary 30 per cent, and in the early secondary stage 33 per cent. Thus it appears that the central nervous system may be invaded at the time of the original generalized dissemination of the *T. pallidum*, or at the time of a subsequent widespread diffusion.



such as occurs in secondary relapse. In either event, the central-nervous-system invasion occurs in the earlier years of the infection. Thus, if infection of the nervous system takes place, the manifestations, as shown by abnormal spinal-fluid findings, will appear within the years during which secondary relapse may be expected. For practical purposes this places neuraxis invasion within the first four years of the infection. It is generally accepted that if the spinal fluid is negative four years following infection, neurosyphilis is extremely unlikely to develop.

Apparently early invasion is controlled in most instances by the immune processes of the host, or by antisyphilitic treatment. Late manifestations of clinical neurosyphilis are relatively uncommon in contrast to the frequency of central-nervous-system invasion by the *T. pallidum* noted above. It has been postulated that there is a neurotropic strain of the organism which has a predilection for nervous tissue. Others have presumed that a familial susceptibility exists to account for such a localization. There is little information to substantiate these two concepts. Reference to Bruusgaard's table in Chapter ix suggests the low incidence of clinical neurosyphilis, and, as Sowder pointed out, these figures are weighted in favour of neurosyphilis by the fact that much of the material was collected from insane asylums. No accurate statistics are available (and probably never will be) as to the incidence of clinical neurosyphilis in untreated syphilis. All figures from clinics or hospitals represent selected cases since these places attract persons who have complaints. However, it is generally estimated that about 5-10 per cent of untreated syphilitic patients will develop neurosyphilis. If anything, this figure probably needs to be graded downward.

Evidence of invasion of the neuraxis by the *T. pallidum*, or its continued

TABLE XXXIV

THE CHARACTERISTICS OF ABNORMAL SPINAL FLUIDS AS TO TYPE  
(MODIFIED AFTER O'LEARY)

Type	Globulin	Cells	Wassermann			Colloidal Curve
			1 cc	0.5 cc	0.2 cc	
I	Negative or positive	10-40	Neg	Neg	Neg	0000000000
II	Positive	10-100+	Pos	Dbt	Neg	0000000000
			Pos	Pos	Neg	2100000000
			Pos	Pos	Pos	0000000000
III	Positive	10-100+	Pos	Pos	Pos	55554432100

activity there, may be obtained only by spinal-fluid examination in the stage of asymptomatic neurosyphilis. In the symptomatic stage it may be diagnosed by the clinical picture, with verification by spinal-fluid abnormalities, except for an occasional case of *tabes dorsalis*. Spinal-fluid changes are usually classified by "grades" or "types." The classification is made on the basis of the interrelationships of the Wassermann test (in several dilutions), globulin, number of cells, and the colloidal test. (The significance of each of these was discussed in the chapter on serodiagnosis.) The Type I spinal-fluid change is seen practically only in acute syphilis. The other two types occur in asymptomatic as well as clinical neurosyphilis.

### INDICATIONS FOR SPINAL-FLUID EXAMINATION

A discussion of the indications for spinal-fluid examination is certain to raise controversial points. It is commonly said by syphilologists and emphasized by the Co-operative Clinical Group that several spinal-fluid examinations should be carried out in every early case of syphilis. The Group states that "tests should be made in cases of early syphilis during the first six months of treatment, and they should be repeated at three-month intervals if positive," and that "examination of the spinal fluid should be made in all cases irrespective of the blood findings before patients are dismissed from treatment." This schedule for spinal-fluid examinations is set up by those working in hospital clinics staffed by highly trained personnel, and under circumstances in which patient-physician relationships are not very close. Furthermore, these men are working in large cities where a severe postlumbar puncture headache in a patient does not become widely known. However, one must be practical about the matter, and make an attempt to keep the number of spinal punctures to a minimum and still obtain essential information.

First, the great majority of syphilitic patients in the United States must be treated by general practitioners or health officers. Secondly, the majority of these physicians either cannot do lumbar punctures or will not assume the responsibility for them. (I am aware of instances in which the local profession condemns a health officer for doing lumbar punctures.) Commonly, the physician must send his patients to some centre for spinal-fluid examinations, and this may be a financial hardship. Thirdly, since the majority of the patients live in small communities, the severe post-lumbar puncture headaches, if they occur, become common knowledge. The occurrence of such a reaction in a public-health clinic may be marked by a sharp decline in patient attendance. However, I wish to emphasize that severe postpuncture headaches are so rare that they offer no excuse for not doing spinal punctures.

Therefore, common sense dictates that spinal-fluid examinations should

be kept to a minimum in the handling of syphilitic patients. (Moore feels that adequate treatment in early syphilis reduces the probability of neurosyphilis to 1 or 2 per cent.) If a positive spinal fluid is found upon examination at the sixth month of treatment in acute syphilis, the therapeutic scheme is not altered until at least a year or more of treatment has been given. Since this is true, this spinal-fluid examination can be dispensed with, and reliance can be placed upon the one which must be done at completion of the treatment for early syphilis.

In early syphilis the danger of relapse is constantly present, especially in the case of inadequate treatment due either to inadequate dosage of arsenic by the physician, or to irregular attendance of the patient. Mucocutaneous relapse or recurrence is always accompanied by serorelapse if the blood test has become negative. Since neurorelapse is a possible form of recurrence, serorelapse, following a period of seronegativity, demands another examination of the spinal fluid even though a previous one was negative.

Only occasionally will one treat an acute case of syphilis in which the blood tests remain positive in spite of adequate treatment (Presumably in such an event the spinal fluid will have been found to be negative at the time of probation.) If such a patient remains "Wassermann fast," spinal-fluid re-examination is indicated after one or two years' probation.

In late syphilis, it is generally accepted that in the absence of treatment, the tissue immunity has been developed to such a degree that redissemination of treponemata is extremely unlikely after four years of infection. Therefore, if the spinal fluid is found to be negative in a patient having had syphilis for more than four years, it is unnecessary again to examine the spinal fluid. A negative spinal fluid in such a case gives almost certain assurance that the patient will not develop clinical neurosyphilis, with the exception of a rare case of cerebral syphilitic endarteritis. In early syphilis, a negative spinal fluid at the end of adequate treatment is almost as good assurance of no subsequent central-nervous-system trouble. Moore found that only 5 per cent of such cases developed neurosyphilis—of a mild type.

With the above points in mind, *the indications for spinal-fluid examination may be summarized as follows:*

1. Before the completion of adequate treatment in early syphilis. Lumbar puncture should be done at some time between one year after the onset of treatment and its completion. If positive, the patient has neurosyphilis, and subsequent spinal-fluid examinations will be indicated as outlined in the appropriate section to follow.

2. If serologic fastness is present after six months' adequate treatment in early syphilis. Seroreversal of the blood is the rule with three to six

months' adequate treatment in early syphilis. Serologic fastness beyond this time is most often due to neurosyphilis.

3 In the presence of persistent serologic fastness in early syphilis on probation after treatment. Spinal fluid re-examination should be carried out after one year's probation.

4 In the event of serorelapse in any case of early syphilis even though a previous negative spinal fluid was obtained. In any patients with early syphilis, in whom the blood test again becomes positive, clinical relapse is a possibility. The relapse phenomenon may take the course of neuro-recurrence as well as that of mucocutaneous relapse. The need for spinal-fluid re-examination is thus apparent. As was indicated in Chapter VIII, secondary recurrence may occur within the first two years after the cessation of treatment.

5 As part of the diagnostic survey in every case of late syphilis unless contraindications exist. The status of the spinal fluid should be ascertained early in the course of antisyphilitic treatment, or before treatment in the late case. If negative, it need never be repeated except in exceptional cases. Among the contraindications are coincident disease with a poor prognosis, such as heart failure. Pregnancy is a contraindication—not in itself, but because of lay opinion, since miscarriage or premature birth following a spinal puncture would certainly be blamed upon this procedure. Therefore lumbar puncture usually should be delayed until after delivery.

6 In the management of neurosyphilis, asymptomatic or symptomatic. Repeated spinal-fluid examinations will be necessary for the evaluation of therapy.

## ASYMPTOMATIC NEUROSYPHILIS

Asymptomatic neurosyphilis is the state in which the spinal fluid shows abnormalities in the absence of clinical symptoms and signs of central-nervous-system disease. Therefore it can be diagnosed only by routine spinal fluid examination. The asymptomatic stage dates from early in the infection to that time when clinical manifestations may appear—from a few to many years later. *Therefore spinal-fluid examination is imperative at some stage in the course of the management of the syphilitic patient.*

### INCIDENCE

The Co-operative Clinical Group study included 5,293 syphilitic patients, in whom spinal fluid examination had been done and who had been observed for two years. Of these, 46.6 per cent were found to have a negative fluid, 39.9 per cent had a positive fluid, with clinical evidence of neurosyphilis, and in 13.5 per cent asymptomatic neurosyphilis was present. This study apparently showed asymptomatic neurosyphilis to

TABLE XXXV

THE DISTRIBUTION OF ASYMPTOMATIC NEUROSYPHILIS ON THE  
BASIS OF RACE AND SEX

		<i>Total Cases Asymptomatic Neurosyphilis</i>	
Co-operative Clinical Group		712	
Vanderbilt University Hospital		172	
<i>White</i>		<i>Coloured</i>	
<i>Male</i>	<i>Female</i>	<i>Male</i>	<i>Female</i>
423 (59.4%)	197 (27.6%)	43 (6%)	49 (6.8%)
58 (33.7%)	39 (22.6%)	41 (23.8%)	34 (19.8%)

be less common in the Negro than in the white race, though no statement was made relative to the proportionate racial admissions to the clinics

Among 6,259 cases admitted to Vanderbilt University Hospital Syphilis Clinic there were 172 patients diagnosed as having asymptomatic neurosyphilis. The proportion of coloured to white patients was 1:13, whereas the proportion of all cases admitted to the clinic was 2:1, respectively. The duration of the asymptomatic state is indicated by a division of the cases into early and late groups, on the basis of less than, or more than two years—sixty seven of the 172 cases were classified as early and 105 as late.

In the discussion of latent syphilis it was emphasized that the diagnosis of latency could not be established until spinal fluid examination had been carried out. Of the cases admitted to the Vanderbilt University Hospital Syphilis Clinic and found free of clinical syphilis, 1,005 were subjected to lumbar puncture. The spinal fluid was negative in 833, and positive in 172 of these. Thus, about 17 per cent of apparently latent cases were found to have asymptomatic neurosyphilis. Moore and Faupel report a frequency of about 13 per cent of positive spinal fluids in 1,216 cases of late syphilis, exclusive of cases of clinical neurosyphilis. Since the asymptomatic state is the forerunner of clinical involvement of the central nervous system, it is evident that spinal fluid examination is essential in every case of syphilis.

The relationship of asymptomatic neurosyphilis to the amount of anti-syphilitic treatment and to the type of treatment plan used before central nervous system invasion was discovered is of extreme importance, as shown by Table XXXVI, taken from the Co-operative Clinical Group study. In its evaluation it must be recognized that Types I, II, and III

TABLE XXXVI<sup>1</sup>  
 AMOUNT AND SCHEME OF TREATMENT BEFORE DETECTION OF NEUROSYPHILIS  
 BY EXAMINATION OF THE SPINAL FLUID<sup>2</sup>

Amount of Treatment	Scheme of Treatment and General Classification of Case									
	Continuous			Intermittent			Irregular			
	Heavy	Nega- tive	Asymplo- matic	Symplo- matic	Nega- tive	Asymplo- matic	Symplo- matic	Nega- tive	Asymplo- matic	Symplo- matic
Arsenic										
Little		72.5	14.1	13.4	82.2	12.0	5.8	73.9	18.1	8.0
Little		85.2	9.9	4.9	86.3	10.5	3.2	68.1	17.0	14.9
Much		90.3	7.5	2.2	82.8	12.7	4.5	74.2	22.6	3.2

<sup>1</sup> From the Co-operative Clinical Group, Ven. Dis. Inform.

<sup>2</sup> Continuous treatment means prolonged treatment without rest periods, consisting of alternating courses of an arsenical and heavy metal, or their use simultaneously.

Intermittent treatment is defined as treatment with an arsenical and heavy metal with rest periods of 4-6 weeks after each course.

Irregular treatment is that not approaching either of the other two

As applied to the number of injections given, "little" means less than twenty injections, and "much" indicates that twenty or more injections were given

spinal fluids are reversed only with increasing amounts of treatment respectively

A very important fact has been pointed out by Moore and Faupel in making a comparison of early and late asymptomatic neurosyphilis with respect to treatment before spinal puncture. They showed that asymptomatic neurosyphilis is three times more common if treatment is irregular in early syphilis, and that Type III fluids are ten times more common in those cases permitted to lapse treatment. These ill effects of irregular treatment are not seen in late syphilis where host immunity already has become established.

As has been indicated in earlier chapters, there is commonly a relationship between serologic fastness and a positive spinal fluid in early syphilis. If, under continuous treatment and adequate arsenic dosage, the blood tests do not reverse (within six months) the clinician should suspect asymptomatic neurosyphilis. The Co-operative Clinical Group material showed that persistently positive blood tests were associated in 74 per cent of instances with a positive spinal fluid. This relationship is not true in late syphilis.

However, it must be pointed out that serologic fastness is not a necessary concomitant of asymptomatic neurosyphilis. In the Co-operative Clinical Group cases, it was found that the blood tests were negative in one-third of the cases of early asymptomatic neurosyphilis under treatment. When treatment is stopped, there is a great tendency to serorelapse in these cases. About one-fifth of the cases of late asymptomatic neurosyphilis showed negative blood tests. *Thus negative blood tests in treated syphilitic patients do not rule out the possibility of neurosyphilis.*

#### PROGNOSIS

The prognosis in asymptomatic neurosyphilis is intimately related to the grade of spinal-fluid change. O'Leary, from a study of the Co-operative Clinical Group material, has presented an excellent exposition of the factors concerned in the outcome of neurosyphilis. He indicated that the grade of spinal-fluid change is a measure of the host's defence mechanism. The milder the change, the more amenable is the condition to treatment, *and the tendency to clinical progression is lessened. Thus, O'Leary found that in 84 per cent of asymptomatic cases with a Type I spinal fluid, reversal takes place with routine therapy—this in contrast to reversal of the fluid with all types of treatment in only 46 per cent of the instances of Type III fluids. Furthermore, this author found that in cases of asymptomatic neurosyphilis 50 per cent of Type I fluids are reversed by one year's routine treatment, the same proportion of Type II fluids*

are reversed by two years' treatment, and that only 40 per cent of Type III fluids are reversed by the end of ten years' treatment

An analysis of the degree of spinal fluid change as related to clinical progression presents another angle of the prognosis in asymptomatic neurosyphilis. Thus, O'Leary found that clinical progression occurred in only 2 per cent of the Type I cases, in 6.5 per cent of the Type II cases, and in 9 per cent of the Type III cases. Moore and Hopkins, in a study of cases followed for eight years at Johns Hopkins Hospital, came to similar conclusions. In 405 cases with negative spinal fluids, only 3.6 per cent developed evidence of neurosyphilis, all being meningeal or meningo-vascular. Of seventy-three cases of asymptomatic neurosyphilis with a Type II fluid, 32 per cent developed symptomatic neurosyphilis, whereas 73 per cent of thirty-six cases with Type III fluid developed neurosyphilis. Thirty per cent of these thirty-six cases had developed tabes dorsalis or paresis.

During the early years of the syphilitic infection there is an increasing resistance to neurosyphilis. O'Leary found that in untreated syphilis spinal fluid changes occurred in 33 per cent of cases within the first year, 24 per cent in untreated syphilis of two years' duration, 20 per cent at the end of three years of syphilis, and in untreated syphilis of four years' duration less than 10 per cent. However, the incidence of symptomatic neurosyphilis increases from this time on.

Relative to these figures it is worthy of comment that the drop in incidence of neurosyphilis in the untreated syphilitic patient in the early years of the infection is in the group of patients having the milder spinal fluid changes. The patients with Type II and Type III fluids contribute heavily to the group of cases with asymptomatic neurosyphilis having persistently positive spinal fluids three or four years after infection. By the tenth year, according to the Co-operative Clinical Group figures, the patients with a positive spinal fluid show an incidence of 56 per cent of symptomatic neurosyphilis, 62 per cent at fifteen years, and 56 per cent at twenty years. The prognosis in the presence of persistently positive spinal fluid is therefore gloomy.

## SYMPTOMATIC NEUROSYPHILIS

When the invasion of the central nervous system by *T. pallida* is accompanied by sufficient involvement of the tissues to impair normal function, clinical neurosyphilis results.

The frequency of clinical neurosyphilis has been placed by various authors at from 20-30 per cent of all untreated syphilitic patients. Moore states that about 5 per cent of all untreated patients may be expected to develop general paresis, an equal proportion tabes dorsalis, and some 15



per cent meningovascular syphilis. He emphasizes that adequate treatment of early syphilis will reduce the frequency of meningovascular disease to 1 or 2 per cent. However, he admits that the two severe forms of late neurosyphilis may occur in a small percentage of cases in spite of routine and adequate therapy in early syphilis, and that only special treatment methods will reduce this frequency.

In general clinical neurosyphilis makes itself manifest some years after infection. An exception to this rule is acute syphilitic meningitis which usually appears as a relapse phenomenon in early, inadequately treated syphilis.

The central nervous system is derived from two embryonal sources. Structures derived from the mesodermal layer are the meninges and the blood vessels. The nervous tissue itself is of ectodermal origin. Thus there may be disease primarily of mesodermal structures (*meningovascular syphilis*), or disease primarily of tissues of ectodermal origin (*parenchymatous neurosyphilis*)—*tabes dorsalis* and *general paresis*. The former represents an inflammatory process, the latter a degenerative one. Admixture of the two is almost certain to occur.

#### MENINGOVASCULAR SYPHILIS

Basically, the pathology in this condition is vascular, but the symptoms may be related only to the involvement of the meninges. However, the syphilitic process may extend into the substance of the brain via disease of blood vessels within the brain. The pure meningeal lesion may be acute or subacute.

Acute syphilitic meningitis occurs in the early months or years of syphilitic infection. Most often it is found in persons who have had inadequate antisyphilitic treatment, and who develop the manifestations of acute meningitis as a relapse phenomenon during a lapse of treatment. Rarely acute syphilitic meningitis may occur while the patient is under treatment with adequate dosage of arsenic. Such cases represent resistance to treatment.

Subacute or chronic syphilitic meningitis occurs from several to fifteen or more years after infection. The purely vascular lesion will be found most commonly within this same period of time.

**Frequency.** Some indication of the frequency of meningovascular syphilis was given earlier in the chapter. It is believed that from 10-15 per cent of untreated syphilitic patients will develop such a manifestation. Among 6,259 cases of syphilis admitted to the Vanderbilt University Hospital Syphilis Clinic, there were 528 cases of neurosyphilis of which 112 fell into the meningovascular group. Fifty-five of these were classified as acute syphilitic meningitis. The remainder represented later manifesta-

tions, of which twenty-nine were purely vascular in their clinical picture (These figures do not include patients admitted to the medical wards )

**Pathology.** Mesodermal syphilitic disease represents an inflammatory process. Thus the meninges present an exudative reaction. The pia arachnoid is usually involved, but the dura may be included in the process as well. Grossly, the changes in the meninges may be so slight that they can hardly be noticed. The meninges present a slight haziness, at times a glutinous exudate at the base of the brain, and less commonly creamy pus. In the forms of meningitis beyond the acute stage, the involvement may be diffuse, or may be represented by patches which are of a milky white colour. The dura mater may be involved extensively. In instances of late meningitis gummatous nodules may at times be found in the meninges adjacent to blood vessels. Chronic productive leptomeningitis, patchy or rather diffuse, may be seen in later stages.

Microscopically, the exudate consists of lymphocytes and a few plasma cells. In a very acute process a number of polymorphonuclear leukocytes may be present. Perivascular distribution of the cellular exudate is characteristic, the round cells appearing as an infiltrate in the lymph spaces of the adventitia of the vessels. There is an associated endarteritis which may become obliterative to give rise to the clinical picture of cerebrovascular syphilis described below. The cellular exudate in the meninges and perivascular spaces may be accompanied by gross, milary, or microscopic gumma formation. Extension of the syphilitic inflammatory reaction along the subarachnoid vessels leads to actual encephalitis in the case of the brain, or myelitis in the cord.

In order that the great variety of clinical pictures which may occur in meningovascular syphilis may be understood, a word as to sites of common involvement is indicated. Often the exudative process is localized to the base of the brain. Under such circumstances cranial-nerve involvement with attendant symptoms may be prominent. Again, the meningeal process may be at the convexity of the cerebrum producing a different set of symptoms. Pure vascular lesions may be limited to one artery, or may be more diffuse. Under such circumstances the clinical picture obviously may be varied.

**Symptoms and Signs.** In the meningitis of syphilis, the symptoms are often those of mild headache, vertigo, and malaise. The manifestations, however, may be more severe with intense headache, stiffness of the neck, nausea, vomiting, and blurred vision. If the meningitis is limited to one side, the pain may be unilateral. Epileptiform seizures may occur, of either the focal or the generalized types, due to patches of chronic productive leptomeningitis. There may be paresthesias and pain. Somno-

lence may occur, and an unconscious state may supervene. Again there may be delirium and excitement. Mental disturbance consists of apathy, anxiety, irritability, memory disturbances, and personality changes.

With basilar meningitis the symptoms often are related to the cranial nerves. Thus with the involvement of the optic nerves blurred vision may be a complaint. Diplopia, ptosis, facial paralysis, tinnitus, and speech difficulties may be complaints.

The signs of syphilitic meningitis also will vary depending upon the severity of the process and its localization. Thus in the milder forms, though the patient may have headache, vertigo, and the like, and spinal-fluid findings compatible with the diagnosis of acute syphilitic meningitis, the physical examination may be entirely negative. However, there may be a low-grade fever. Cervical rigidity may be demonstrable, as well as a positive Kernig sign. Occasionally there may be patellar clonus and increased deep reflexes. The pupils may be found to be irregular, unequal, and to react sluggishly to light. In basilar meningitis the signs will be dependent upon the cranial-nerve involvement. In the event of optic neuritis, papillitis may be demonstrable by ophthalmoscopy. Contracted visual fields may occur. Secondary optic atrophy with blindness is at times the end result of such involvement of the optic nerve. Ptosis and paralysis of extra-ocular muscles are not uncommon, facial paralysis is also not infrequent. Usually these manifestations are unilateral, but may be bilateral. Deafness due to involvement of the eighth cranial nerve may occur. (Signs of involvement of the cranial nerves beyond the eighth more often imply involvement of the brain stem rather than a meningitic process.)

Cases 52, 85, 86, 87, 88, 89, and 98 offer examples of some of these clinical entities.

**Case 85.** A twenty year-old white male was seen on January 15th and 22nd as a sexual contact of a patient with acute syphilis. On both occasions Wassermann and Kahn tests were negative. On February 6th he was found to have two small superficial ulcers on the glans penis of six days' duration. An enlarged right inguinal node was noted two days before admission. *T pallida* were found in the lesions. Blood Wassermann and Kahn tests were negative.

Arsphenamine 0.3 Gm. and bismuth were given, and treatment missed until February 22nd. The lesions had healed. Blood Wassermann test was negative, Kahn test positive. In the next eighteen weeks the patient received arsphenamine 0.4 Gm.  $\times 2$ , neoarsphenamine 0.6 Gm.  $\times 10$ , bismuth  $\times 7$ . (Neoarsphenamine was used because of reactions to arsphenamine.) Treatment lapsed from June 28th to August 9th. The patient then returned because of recurrent penile lesions, severe headache, pain in the eyes, and vertigo.

Examination revealed extensive edema of the prepuce, making examination of the glans impossible. Blood Wassermann and Kahn tests were positive.

Spinal-fluid examination showed increased globulin, 20 cells per cu mm, Wassermann positive in all dilutions, colloidal mastic test negative

**Comment.** As the result of contact investigation a chancre of six days' duration was found, and treatment was begun in the seronegative stage. Because of lapse of treatment positive serologic tests developed in the blood and spinal fluid, in addition to the mucocutaneous relapse. This represents mild acute meningitis as a relapse phenomenon.

**Case 86.** A twenty-four-year-old Negro was admitted to the Genito urinary Clinic because of a penile lesion of two or three weeks' duration. He was seen in the Syphilis Clinic after a dorsal slit operation. A hard plaque was found at the corona. Inguinal adenitis was present. *T pallida* were found in serum from the lesion. Blood Wassermann and Kahn tests were positive.

The patient received arsphenamine 0.4 Gm  $\times 3$ , and then stopped treatment. He returned eight weeks later because of headache of three weeks' duration, this was worse at night. He also complained of vertigo and pain and stiffness of the neck. A tooth had been extracted because of the headache.

Examination revealed tenderness of the neck, and pain on passive movement. Blood Wassermann and Kahn tests were positive. Spinal fluid showed cells 980 per cu mm (mostly lymphocytes), increased globulin, Wassermann test positive in 1:0, 0.5, and 0.2 cc, and a mastic curve of 5554321000.

He then received regularly arsphenamine 0.4 Gm  $\times 13$ , and bismuth  $\times 6$  and iodides. The symptoms of meningitis disappeared promptly.

Treatment was again lapsed. He returned eight years later because of headache of two weeks' duration. Examination revealed irregular pupils, reacting sluggishly to light. The blood Wassermann test was positive, the Kahn test negative. Spinal fluid showed cells 99 per cu mm, increased globulin, Wassermann test positive in 1:0, 0.5, 0.2 cc, and a mastic curve of 3211000000.

He was given clorarsen 0.67 Gm  $\times 19$ , and bismuth  $\times 9$ . Treatment lapsed for five months, following which, nine years after his neurorelapse, the spinal fluid showed cells 40 per cu mm, increased globulin, Wassermann test positive in 1:0 and 0.5 cc, negative in 0.2 cc, and a mastic curve of 3210000000.

**Comment.** This patient presented acute syphilitic meningitis as a neurorelapse with onset of symptoms five weeks after the lapse of treatment given for seropositive primary syphilis. Following a subsequent lapse of eight years, the spinal fluid still showed evidence of active neurosyphilis, and the pupillary signs of early tabes dorsalis were present.

**Case 87.** A thirty-six year-old white man was admitted to the Medical Clinic because of pains in the lower extremities, these had appeared two weeks before. Pains were referred to the lumbar region, hips, knees, and especially to the legs. Though his memory used to be bad, he believed he was 'a million per cent better'. He had been taking antisyphilitic treatment for one year before admission. The patient's wife stated that he had a definite memory defect, was irritable, that he was well satisfied with himself, and that he had spells of mental confusion. He had had a penile lesion ten years before.

Examination disclosed the pupils to be unequal in size, but reacting to light and accommodation. Tendon reflexes were absent in the lower extremities.

Romberg test was positive, and the vibratory sense was abnormal. Blood Wassermann and Kahn tests were negative. Spinal fluid showed increased globulin, cells 1 per cu mm, Wassermann test positive in 1.0 and 0.5 cc, doubtful in 0.2 cc., with a negative mastic curve.

Arsphenamine 0.3 Gm  $\times$  15, and bismuth  $\times$  19 were given regularly. Though the lightning pains improved, his wife felt the mental condition was becoming worse. He was inoculated with tertian malaria, and was allowed to have nine paroxysms, in addition to a four-day period with a temperature ranging from 102.5° to 103° before paroxysms began. In the following two years, the patient received arsphenamine 0.3 Gm  $\times$  26, tryparsamide 3.0 Gm  $\times$  21, bismuth  $\times$  47 rather irregularly. He had recurrent bouts of lightning pains. At the end of this time the spinal fluid was negative in all respects, and the blood tests were negative.

The patient returned at the end of one year because of lightning pains. At this time the patient's wife mentioned, for the first time, seizures which had begun four years before (1.5 years before the patient was first seen at the clinic). The attacks were characterized by sudden awakening from sleep and a stream of unintelligible words. In the daytime, if attacks came on while driving his truck, he would take his hands off the wheel and feet off the pedals and appear to be unconscious for a few seconds. The wife accompanied him on all his drives so she might grasp the wheel. Each attack ceased with his asking the date.

He was given iodides and bismuth  $\times$  11, and again was not seen for eighteen months when he returned because of increasing convulsive seizures. He had such an attack while being examined in the clinic. It lasted for two minutes. His face became contracted, the left arm showed tonic contractions, and a few clonic ones. There was urinary incontinence. He walked the floor aimlessly, then slid to the floor, sitting under the examining table. He then became aware of his position, got up and asked for a cigarette. His wife said he was having one to two attacks daily. Spinal fluid examination was completely negative.

Dilantin 0.1 Gm was prescribed three times daily. He has now been on this drug for 2.5 years, taking only 0.1 Gm a day. There have been no recurrences of convulsive seizure except once when he was out of the drug. Now, eight years after fever therapy and the use of dilantin, he is comfortable, carrying on his business as a fruit peddler. Examination reveals sluggish pupils and absent reflexes.

**Comment.** The diagnosis of taboparesis seems justified. The absence of a characteristic parietic spinal fluid on admission can be explained by the fact he had had previously eighteen months of chemotherapy. The parietic process was stopped by fever therapy. Lightning pains also improved. The *Jacksonian* attacks are due to meningeal scar from the old meningo-encephalitic process.

Syphilitic vascular lesions of the brain may be either truly such or associated with meningeal changes so that the clinical picture is a mixed one. Therefore if I limit myself to a description of the common vascular syndromes, it must be understood that these may be associated with the meningeal symptoms and signs which have been just described. Obliterat

ing syphilitic endarteritis produces clinical manifestations differing in nowise from those produced by nonsyphilitic thrombosis, by hemorrhage, or by cerebral arteriosclerosis

The mulder forms of endarteritis are associated, not with complete obstruction to blood flow, but to a partial one producing temporary ischemia. In such instances attacks of transient paresis or paralysis of one or more extremities may occur, or there may be a temporary clouding of consciousness. These attacks, either motor or mental, are often of ten to twenty minutes' duration. The following case is an example of meningovascular syphilis.

**Case 88.** A fifty seven year-old white man was admitted to the Otolaryngology Clinic because of vertigo and impairment of hearing. About 1.5 years before he suddenly became so dizzy that he was unable to walk for some minutes. At about the same time he had "four strokes" separated by short intervals. In each episode he lost complete use of the left side of the body, once for thirty minutes, in the remainder for ten minutes each. Recovery from the paralysis was complete each time, consciousness was present during the attacks. Diplopia occurred at times. The vertigo had incapacitated him greatly and had forced him to remain in bed for the five days before admission. Tinnitus and gradually progressive loss of hearing began at the onset of symptoms. A weight loss of 20 lb. occurred during the illness. The patient could give no history of acute syphilis.

Examination showed that the pupils reacted well, but were unequal in size due to a traumatic cataract of the left eye present since the age of eight years. Eighth nerve deafness was present. The knee-jerks were absent. Blood Wassermann and Kahn tests were positive. Spinal fluid showed increased globulin, cells 16 per cu. mm., Wassermann test positive in 10, 0.5, 0.2 cc., and a 5554321000 mastic curve.

The patient received regularly bismuth  $\times 20$ , and neoarsphenamine 0.6 Gm  $\times 24$ , at the end of which time the spinal fluid showed increased globulin, cells 5 per cu. mm., Wassermann test positive in all dilutions, and a 3210000000 colloidal mastic curve. Treatment continued with additional bismuth  $\times 42$ , tryparsamide 3.0 Gm  $\times 4$ , and neoarsphenamine 0.6 Gm  $\times 22$ . (Tryparsamide was discontinued because of visual complaints, since he was already blind in one eye, no further attempt was made to use the drug.) Following this treatment, spinal fluid showed globulin to be slightly increased, cells 2 per cu. mm., Wassermann test positive in 10 and 0.5 cc. and negative in 0.2 cc., and a negative colloidal test.

During the next 2.5 years, three courses of bismuth  $\times 12$  and iodides, with intervening rest periods of five months, were given. The spinal fluid then showed a trace of globulin, no cells, Wassermann tests positive in 10 cc., negative in 0.5 and 0.2 cc., and a negative colloidal test.

The patient improved progressively after treatment was begun, he gained weight. Vertigo had disappeared completely at the end of five months' treat-

ment Tinnitus and hearing improved, though some residue remained. Transient hemiplegia never recurred. The blood Wassermann test became reversed within four months, but the Kahn test always remained either doubtful or positive.

**Comment** Conservative treatment was necessary in this fifty-seven year-old man, who was in rather poor physical condition. However, symptomatic cure was obtained with marked improvement in the spinal fluid findings. Now in his early sixties, he is active and feeling well.

Hemiplegia ( 'stroke ' ) may be of sudden onset, with or without loss of consciousness (cases 92 and 93). Or, the onset may be gradual and without loss of consciousness. This most commonly recognized syphilitic vascular accident in the brain is due to involvement of the lenticulostriate artery. Obviously other vessels may be affected causing other syndromes, but textbooks of neurology should be consulted regarding these since the scope of this volume precludes the discussion of the rarer lesions.

The physical findings associated with syphilitic endarteritis of the lenticulostriate artery are the same as those in disease of this vessel on a hypertensive or arteriosclerotic basis, and so are familiar to the reader. Weakness or paralysis of the muscles of one side of the body occurs. Increased deep reflexes, a positive Babinski sign, and absent abdominal reflexes are then found. Involvement of the left lenticulostriate artery may be followed by aphasia. A spastic gait may result. Pains in the affected extremity often are present. The clinical picture is so like that due to nonsyphilitic cerebral vascular accidents, which are so common, that a case report seems unnecessary.

**Laboratory Findings** The blood tests are usually positive for syphilis in cases of meningovascular involvement but not necessarily so. In acute syphilitic meningitis (and in that form representing neurorelapse) it safely may be said that the blood tests are always positive. In late meningitis the blood may not be so strongly positive, and may even be negative. Purely cerebral vascular lesions may be associated with negative blood tests.

The spinal fluid findings in very early cases of meningeal irritation may be no greater than those characteristic of Type I fluids. Usually, the spinal fluid changes will be of the Type II variety. The highest cell count will be found in acute syphilitic meningitis, in which the count may be in the hundreds, approaching or even exceeding 1,000 cells per cu mm. Though the cells in the spinal fluid in neurosyphilis are usually lymphocytes, in the high-cell counts of acute syphilitic meningitis, polymorphonuclear leukocytes may appear to a fair percentage. This is a reflection of the intensity of the meningeal reaction. In meningitis occurring years after infection, the cell count is usually less than 200 cells per cu mm. Often

the pleocytosis is of very moderate degree. The Wassermann reaction is variable in syphilitic meningitis, varying from a low to a high titer.

In purely syphilitic vascular lesions of the cerebrum, the cells in the spinal fluid are usually only slightly increased, if at all. Often the Wassermann reaction is of low titer, and occasionally is negative.

Though the spinal fluid findings more often than not are of the Type II variety in meningovascular syphilis, this is not necessarily true, for a Type III fluid may be found in some instances. Here the positive Wassermann in a high titer and the paretic curve in the colloidal test indicate a more grave prognosis. It may foreshadow parenchymatous neurosyphilis, or may actually indicate its presence at the moment, since the manifestations of meningovascular syphilis may be encountered in the tabetic and the paretic patient.

**Differential Diagnosis.** Central nervous system disease in a young or relatively young adult should always raise the question of neurosyphilis. Fortunately the laboratory is practically always of value in establishing the part syphilis may play in the clinical picture. A positive blood test, unless there has been recent antisyphilitic treatment, is usual in meningovascular syphilis, though it must be recognized that in late cases (of ten to fifteen years' duration) such tests may be negative. In any event, the spinal fluid examination will practically always give findings compatible with neurosyphilis, though in purely vascular lesions, especially if previous antisyphilitic treatment has been given, a negative fluid rarely may be encountered.

In the diagnosis of meningovascular syphilis, the history is of importance. A history of recent syphilis and lapsed treatment are of exceptional significance in face of symptoms which might be those of acute syphilitic meningitis. A history of syphilis, with or without treatment, should be inquired into in the presence of cranial nerve involvement, chronic headache, personality changes, and vascular accidents—especially, since in cases of some years' duration treatment may have led to negative blood tests for syphilis.

The conditions from which meningovascular syphilis must be differentiated are numerous. Obviously, this is not a volume in which minutiae of differentiation can be considered. The reader must consult textbooks on neurology for these since only brief mention can be made of the conditions which must be considered in diagnosis.

The symptoms and signs due to increased intracranial pressure and localized involvement, which may occur in brain tumour or abscess, may simulate meningeal syphilis. The laboratory tests for syphilis will be essential in the diagnosis.

Acute meningitis due to the meningococcus or other pyogens is usually



of more sudden onset than in syphilitic meningitis, and has a more marked febrile reaction. It is associated with a blood-stream leukocytosis and with a spinal fluid in which the polymorphonuclear cells predominate in contrast to syphilitic meningitis.

Tuberculous meningitis may closely simulate acute syphilitic meningitis, in its slower onset and prodromal symptoms of headache. Here again the diagnosis must be based on laboratory studies. Virus meningitis may simulate acute luetic meningitis especially because of its relative mildness and the lymphocytic response in the spinal fluid. Lymphocytic choriomeningitis is of this type.

Late meningeal disease due to syphilis may bring up the question of brain abscess or tumour, because of the cortical sites involved. Tumours at the base of the brain may also be simulated because of cranial-nerve involvement. Bell's palsy cannot be differentiated from a facial paralysis due to syphilis except by the spinal-fluid evidences of neurosyphilis.

Epilepsy of the focal or jacksonian type always requires a consideration of syphilis in a search for the cause. Generalized epileptiform seizures may be of syphilitic origin. Of importance in differentiation is the fact that idiopathic epilepsy usually begins in an age-group younger than that in which neurosyphilis is found, but this is not necessarily so.

Vascular syphilis with "stroke" needs to be differentiated from vascular accidents due to other causes. In the absence of hypertension, a vascular accident in a relatively young adult (in the third or fourth decade of life) should suggest the probability of syphilitic endarteritis. An occasional instance of cerebral embolism, most often in the presence of mitral disease, made need to be differentiated from vascular syphilis. In the age group in which arteriosclerosis is commonly encountered, the diagnosis of syphilitic arteritis becomes difficult. Thrombosis in an arteriosclerotic cerebral vessel and syphilitic endarteritis may present identical clinical pictures.

A variety of rare neurologic conditions in addition to those noted above may be simulated by neurosyphilis. Here, as in other fields, the axiom that syphilis may imitate any disease is unquestionably true.

**Prognosis.** In general, with treatment, the outlook in syphilitic meningitis is good. Even without treatment death is rare. Acute syphilitic meningitis responds well to treatment. Chronic meningitis demands a more guarded prognosis. In chronic leptomenigitis with its residual scarring and adhesions in the meninges, focal epilepsy may persist (Case 87). In these instances some encephalitis presumably had been present with resultant scarring in which adherent meninges may be incorporated. At times there is no normal restoration of function where cranial nerves were affected. Optic atrophy may supervene upon the inclusion of the

optic nerve in a basilar meningitis. In most instances the hemiparesis or hemiplegia due to syphilitic endarteritis clears up with antisyphilitic treatment (also often spontaneously), though such may not be the case and residua may persist to some degree. In the vascular type of disease there is always a possibility of subsequent recurrences.

Moore believes that with adequate treatment 80 per cent of cases of acute syphilitic meningitis will attain excellent clinical and serologic results, whereas with poor treatment such results are less than half as good. The poorly treated cases contribute to the tabetic and parietic groups of patients in the later years of the disease. Moore likewise finds that in the more chronic cases of meningovascular syphilis, one may expect arrest of the process in 80 per cent and good serologic results in about 65 per cent of instances by adequate treatment.

#### PARENCHYMATOUS NEUROSYPHILIS

The tissues of mesodermal origin—the meninges and the blood vessels—may be primarily involved in an inflammatory reaction as has been described in meningovascular syphilis. However, even then there may be some degree of encephalitis due to extension of the pathologic process along the blood vessels into the cortex of the brain. Though in parenchymatous neurosyphilis there is involvement of tissues of ectodermal origin (the nervous tissue proper), the process is not restricted to these tissues. Vascular and meningeal inflammatory reaction is concurrent with the parenchymatous degenerative process. *Tabes dorsalis* and *general paresis* are the prime diseases classed as parenchymatous neurosyphilis. Each may be seen as a clear-cut entity, or the clinical pictures may be merged to produce a combination of the two—so-called taboparesis, a state in which the psychotic features are usually not so outspoken as in pure general paresis. The clinical features of meningovascular syphilis may accompany parenchymatous neurosyphilis.

**Tabes Dorsalis (Locomotor Ataxia)** This chronic, usually progressive form of neurosyphilis presents a pathologic process involving the dorsal ganglia and posterior spinal roots with subsequent degeneration of the fibres of the dorsal columns, and of short fibres in the segments of the cord. It appears late in the course of syphilis, may progress for a long time, and then become quiescent spontaneously.

**FREQUENCY** It is estimated that about 5 per cent of untreated syphilitic patients develop *tabes dorsalis*. At the Vanderbilt University Hospital Syphilis Clinic, among 528 cases of neurosyphilis 159 had *tabes dorsalis*, including 38 with primary optic atrophy which is to be considered as a manifestation of *tabes*. A study of 114 of these patients has been made. The distribution as to race and sex was as follows: Negro males 36, Negro

females 12, white males 53, white females 13. The proportion of Negro to white tabetics is 1:13, whereas admissions to the syphilis clinic were in the proportion of 2:1. These figures bear out the usual statement of the higher incidence of tabes dorsalis in males than in females, and in white than in Negro patients.

Tabes dorsalis makes itself manifest most commonly after the first decade of the syphilitic infection. Table XXXVII illustrates the years elapsed from infection to the appearance of symptoms of tabes dorsalis including primary optic atrophy in 114 cases in our clinic.

TABLE XXXVII

TIME ELAPSED FROM INFECTION TO TABETIC MANIFESTATIONS

5-9 Years	6
10-19 Years	34
20-29 Years	19
30-39 Years	5
Congenital, above 15 Years	3
Unknown	47
Total	114

**PATHOLOGY** In light of the pathologic findings some questions have arisen as to the possibility of other factors operating, in addition to syphilis, in the production of tabes dorsalis. The outstanding pathologic change is a degeneration of the nerve fibres of the dorsal spinal roots and of the dorsal columns of the spinal cord, where the fibres are replaced by scar (glial) tissue. The process may also invade the dorsal ganglia. Grossly, in advanced cases, the dorsal roots are found to be small, and due to the loss of substance in the posterior columns, the usual convexity of the dorsal aspect of the cord is replaced by a flattening or even a concavity. The overlying pia and arachnoid meninges may be opaque and adherent.

Microscopic examination demonstrates a degeneration of the fibres of the dorsal column, fibres arising from the nerve cells of the dorsal ganglia. A mild meningeal reaction occurs about the dorsal roots. There is disagreement among pathologists as to whether or not an inflammatory reaction extends as an invasive process between the fibres in the dorsal root. The pathology of tabes dorsalis is not entirely like that of syphilis in general. This may account for some of the inexplicable things which occur in the clinical course of the disease. The presence of the *T. pallidum* has been demonstrated but rarely in the lesions of tabes dorsalis in contrast to the comparative ease of its demonstration in general paresis. Thus in addition to the belief of direct invasion of the dorsal root by the organism, there has been the theory of a circulating toxin reaching the afferent

fibres probably via the perineural lymphatics. By this theory the paucity of the organisms could be explained. One student of the problem feels that treponemata locate at the sharp angle made by the meninges at the junction of the posterior root with the cord, and that a typical syphilitic lesion here leads to a meningeal reaction choking off the root. In recent years, nutritional deficiency has been thought, by some, to play a part in the pathogenesis of tabes dorsalis.

Primary optic atrophy is an accompaniment of tabes dorsalis in a high proportion of cases. Pathologically, it presents a round-cell infiltration in the meninges surrounding the optic tracts. The outer marginal fibres of the tract are involved first by the process.

**SYMPTOMS AND SIGNS** The symptoms and signs in the patient having tabes dorsalis may be few or many. A detailed description of the clinical picture may be found in textbooks on neurology, but the major complaints and findings will be outlined briefly.

Involvement of the dorsal spinal roots results in functional alterations in the sensations. Pain is often prominent, and it is usually spoken of as "lightning pain" because of its characteristic sudden appearance, rapid radiation, and disappearance. Often it is described as radiating from the gluteal region to the heel or foot, though it may be limited to the leg, and less commonly to the arm. The pain may simulate a constricting band about the trunk and under such circumstances is named "girdle pain." If pain is referred to the abdomen and physical examination is careless, a mistaken diagnosis may lead to laparotomy. We have seen one patient who had undergone eight abdominal operations because of tabetic root pain. Pain in the distribution of the trigeminal nerve may occur at times.

With involvement of the sympathetic rami (not proven), visceral crises may occur as paroxysmal, sudden attacks of pain referred to certain organs, persisting from minutes to days and even weeks. These crises may be referred to the stomach, rectum, bladder, larynx, and pharynx. Gastric crises may be accompanied by severe nausea and vomiting, at times lasting for days so that nothing can be retained. At times retching may be so severe that hematemesis occurs.

Sensory disturbances are marked by paresthesia and hypesthesia. The paresthesia is most commonly referred to the soles of the feet, and is described as a sensation of walking on a thick soft carpet. Diminished sensation, even to anaesthesia in some areas, is not uncommon. There may be a "butterfly" area of hypesthesia over the nose. (Often the tabetic is unaware of the insertion of the spinal puncture needle, even though a local anaesthetic is not used.)

Inco-ordination or ataxia is due to the involvement of the fibres of the posterior columns. It is most prominent in the lower extremities. The

patient loses the co-ordinated automatic movements of muscles in walking, so that conscious attention is necessary in this act. The difficulty is exaggerated in the dark. A slapping gait develops with progression of the disease.

With involvement of the sacral roots, disturbances may occur in the organs supplied by this portion of the nervous system. Thus there may be a loss of libido, impotence in the male and sexual anaesthesia in the female are not uncommon. Sphincter disturbances of the rectum and bladder may lead to incontinence of urine or feces.

So-called trophic disturbances, possibly due to sympathetic-nerve involvement, plus the factors of trauma and anaesthesia, lead to such painless manifestations as the Charcot joint (most often seen in the knee, but which may occur in any large joint including intervertebral joints), perforating ulcers of the foot, and spontaneous fractures of bones.

In addition to the trigeminal-nerve pain mentioned previously, such transient motor disturbances as ptosis, diplopia, and the like may occur. The most serious disturbance related to cranial nerves is optic atrophy, which occurs in about 10 per cent of tabetics. *Primary optic atrophy may occur without any other signs of tabes dorsalis.* The patient's complaint is that of progressive failing vision.

The frequency of the symptoms in the 114 tabetic patients studied by us recently is shown in Table XXXVIII. The high incidence of failing vision is explained by the inclusion of ten cases showing primary optic atrophy only.

TABLE XXXVIII

## FREQUENCY OF SYMPTOMS IN 114 PATIENTS WITH TABES DORSALIS

Lightning pains	70
Inco-ordination or ataxia	51
Failing vision	43
Urinary incontinence	28
Visceral crises	15
Loss of libido, or impotence	13
Diplopia	10
Paresthesias	7
Charcot joint	6
Perforating ulcers (mal perforans)	6

Loss of weight and strength are common complaints in tabes dorsalis. Memory loss and other psychic changes, found more often in general paresis, may appear in the history of the tabetic patient. These cases give the combined picture of taboparesis.

The physical examination in tabes dorsalis may reveal little or may

demonstrate many abnormal findings. There is often obvious weight loss. At times one gains the impression of a "smoothed-out" facial expression. One of the earliest and the most frequent sign on examination is the Argyll-Robertson (A R) pupil. This disturbance in pupillary physiology may be unilateral, but more often is bilateral and is permanent. Practically, it is not seen except in neurosyphilis (tabes dorsalis and paresis), and thus is of great diagnostic value. The A R pupil is one that is miotic and does not react to light, but does respond to accommodation. (It is not definitely known in which part of the reflex arc the pathology occurs.) A period of a sluggish reflex reaction to light may antedate fixation to light. In addition to the abnormal light reflex, the pupils may be irregular, or unequal (anisocoria). A "fixed pupil," that is, a pupil which reacts neither to light nor to accommodation, may be seen very late in tabes dorsalis, or in association with optic atrophy. It also occurs in meningovascular syphilis and as was brought out under the discussion of iritis, as the result of adhesions of the iris to the anterior lens capsule.

The most frequent cranial-nerve disturbance is that of atrophy of the optic nerve. Examination with the ophthalmoscope early reveals pallor of the optic disk, and later a chalky whiteness. Other cranial nerve involvement may be manifest by ptosis of the eyelids and ocular palsies. Sensory disturbances may be demonstrable in the distribution of the trigeminal nerve.

The tendon reflexes usually show disturbances. These are usually limited to the lower extremities (knee- and ankle-jerks) but may also be seen in the upper extremities. Due to the posterior-column involvement, there is interference with the reflex arc, and thus the deep reflexes are diminished or sluggish, later becoming absent. The skin reflexes are unchanged. Other evidences of posterior-column involvement are manifest by the loss of vibratory sense, demonstrated by the application of a vibrating tuning fork to a bony prominence. The loss of the sense of position is demonstrable in that the patient is unaware of the position or movement of his toes as they are moved passively. Ataxia, another manifestation of the loss of position sense, is demonstrated by the staggering gait, by the flopping of the legs in walking, and by the Romberg test—swaying or even falling as the patient stands with feet together and eyes closed. The ataxia can be shown also by tests requiring the placing of the finger on the nose, heel on the knee, etc., with and without eyes closed.

Areas of hypesthesia may be demonstrated. Decreased sensitivity may be shown upon squeezing the Achilles tendon or the testicle. Digital examination of the rectum often reveals an atonic anal sphincter. The genito-urinary surgeon upon cystoscopy notes trabeculation and atony of the bladder. The skeletal muscles often show loss of tone.

Less commonly one sees Charcot joints and perforating ulcers. The Charcot joint, which may occur in any of the large joints, usually is found in the knee. Such a joint is enlarged, has demonstrable fluid in it, and shows destruction and fragmentation of bony and cartilaginous tissues with new bone formation. It is painless. Palpation of the moving joint reveals crepitus and crunching, the joint is abnormally mobile, so that the leg may be hyperextended and may be freely moved laterally. Eventually the joint will not support weight. The roentgenogram shows rather characteristic findings. A Charcot joint of the spine, through secondary compression, may produce the symptoms of transverse myelitis. Mal perforans, or penetrating ulcers, are seen on the sole of the foot. They are painless ulcers, penetrating deeply to and into the bones, and are extremely difficult to treat.

Among the 114 tabetics studied by us, the frequency of signs is shown in Table XXXIX. Again the high incidence of optic atrophy is explained by the inclusion of ten cases of faulty vision without other complaints.

TABLE XXXIX

FREQUENCY OF PHYSICAL SIGNS IN 114 PATIENTS WITH TABES DORSALIS

Pupils (A R. or definitely sluggish)	83
Pupils (irregular but react to light)	14
Deep reflexes (absent or sluggish)	78
Romberg test positive	51
Ataxia	46
Optic atrophy	43
Pain sense impaired	18
Vibratory sensation lost	17
Cord bladder	11
Cranial nerve involvement	10
Anal sphincter atony	3

**LABORATORY FINDINGS** The blood tests for syphilis are found to be negative in about one-third of the cases of tabes dorsalis. A realization of this is of great importance, since too often one hears a physician say, "I'd think this was tabes, but the blood is negative."

*The spinal fluid usually reveals abnormalities.* Since there is usually some meningeal reaction, cells and globulin are usually increased but moderately. Often the fluid is of Type II, with a positive Wassermann only in the lower dilutions. The spinal fluid may be of the Type III group, but this is found more often in the patient showing mental abnormalities in addition to tabes dorsalis (taboparesis). Unlike general paresis, the clinical picture of rather marked tabes dorsalis may be associated with a

negative spinal fluid, with or without positive blood tests for syphilis. This condition is commonly spoken of as "burnt-out" tabes. O'Leary found that 5 per cent of the Co-operative Clinical Group cases had a negative spinal fluid at the time of study of the patient. The spinal-fluid changes in our 114 patients with tabes dorsalis or optic atrophy appear in Table XL.

TABLE XL

SPINAL-FLUID FINDINGS IN 114 PATIENTS WITH TABES DORSALIS

<i>Disease</i>	<i>Negative</i>	<i>Type II</i>	<i>Type III</i>
Tabes dorsalis	13	72	18
Taboparesis	—	1	10

Among the thirteen instances in which the spinal fluid was negative, six had had previous antisyphilitic treatment. Of the ten cases of optic atrophy alone, only two had a negative spinal fluid. Of the 101 cases with a positive spinal fluid, blood Wassermann and Kahn tests were negative in 14. Not a single instance of negative blood tests occurred in the eleven taboparetic patients. Among the thirteen cases with a negative spinal fluid in the presence of a clinical picture of tabes dorsalis, there were seven in which the blood was also negative. In this series of cases a negative blood test was found in 18 per cent at the time the patient was first seen at Vanderbilt University Hospital.

**Case 89.** A thirty-eight-year-old Negro entered the Surgical Clinic because of headache and a pulsating mass in the right arm of one year's duration. Vertigo and progressive loss of vision in the right eye had been present for seven months preceding admission. There was a history of several penile sores in the past, the first one twenty years before.

Examination showed that the ophthalmologist found the vision to be O S 20/20, O D counting of fingers only. The visual field in the left eye was normal and could not be obtained on right. The right optic disk was atrophic. The right pupil was Argyll Robertson in type, the left was larger and reacted well to accommodation, but sluggishly to light. On the medial aspect of the right forearm was a nontender, nonpainful reducible tumour the size of a marble, showing expansible pulsation synchronous with the heart. The right knee-jerk was absent. Blood Wassermann and Kahn tests were positive. Spinal fluid showed increased globulin cells 67 per cu mm, Wassermann test positive in all dilutions, and a mastic curve of 4322100000.

The aneurysm was removed surgically. Neoarsphenamine 0.6 Gm  $\times$  30, bismuth  $\times$  27, and iodides were given and the blood Wassermann and Kahn tests reversed. Spinal fluid then showed increased globulin, no cells, Wassermann positive in all dilutions, and a negative mastic test. Headaches



and dizziness were less. The left eye remained normal. The right eye was completely blind.

Treatment was continued with neoarsphenamine 0.6 Gm  $\times$  9, and bismuth  $\times$  10. The last two injections of arsenic were followed by bleeding from the gums, the night following the injection. About fifteen hours after the second episode, examination showed petechiae on the lips, gums, and skin. The patient then was given mapharsen 0.06 Gm  $\times$  8 without recurrence of bleeding, and bismuth  $\times$  21. At the end of this time (one year after the last preceding lumbar puncture) the spinal fluid was negative in all respects.

**Comment** Unfortunately, no pathologic evidence is available to indicate whether the aneurysm of the radial artery was syphilitic. The unilateral optic atrophy, even though in a tabetic, probably represents secondary optic atrophy due to syphilitic meningitis. Headache was associated with this. Of interest was the purpura which immediately followed the use of neoarsphenamine, but did not recur with the use of mapharsen.

**Case 90** A thirty-two-year-old white housewife was referred to the Syphilis Clinic because of "weakness of legs." She noted the onset of weakness of the legs and difficulty in balancing herself three years before. Severe, sharp pain lasting one to two seconds appeared in the calves of the legs and radiated to the ankle. She had fallen several times because of weakness. Urinary incontinence occurred at times. All symptoms were progressing. She had lost 13 lb in weight. There was no history of acute syphilis. Blood Wassermann and Kahn tests were known to be positive six years before, but no treatment was advised. She had been married nine years but had never been pregnant. Her husband was found to be seronegative in both blood and spinal fluid. He gave no history of syphilis.

Examination showed that the right optic disk was somewhat pale, but visual fields were normal. The left pupil reacted sluggishly to light. Deep reflexes in the lower extremities were absent. Marked ataxia was demonstrable in both upper and lower extremities. She was unable to stand alone with the eyes closed. There was loss of the sense of position of the toes. She walked with a wide base, and was unable to walk with the eyes closed. Blood Wassermann and Kahn tests were positive. Spinal fluid showed increased globulin, cells 50 per cu mm, Wassermann test positive in 1:0, 0.5, 0.2 cc, and a mastic curve of 22110000000.

Following neoarsphenamine 0.45 Gm  $\times$  22, and bismuth  $\times$  30 given regularly, the spinal fluid showed increased globulin, cells 1, Wassermann test doubtful in 1 cc and negative in the other dilutions, and a negative mastic test. The lightning pains and urinary incontinence did not recur after the first six months of treatment. She then received regularly neoarsphenamine 0.45 Gm  $\times$  9, mapharsen 0.04 Gm  $\times$  12, arsphenamine 0.2 Gm  $\times$  12, bismuth  $\times$  31. The spinal fluid was then completely negative. Though the blood Wassermann reversed under treatment, the Kahn test always remained positive.

In the second year of treatment after an eight week course of bismuth the patient developed bilateral iritis. Since an injection of neoarsphenamine was followed by a severe nitritoid reaction, mapharsen was used in the subsequent six weeks. Because the iritis appeared and persisted in spite of regular anti-

syphilitic treatment, search was made for foci of infection. Since no relief was obtained by the use of mapharsen, arsphenamine 0.2 Gm per dose was used (dosage of 0.3 Gm caused vomiting). After two injections the iritis cleared up completely. A course of twelve injections of arsphenamine was given. No subsequent relapse occurred.

**Comment** *Tabes dorsalis* might have been prevented in this patient had



FIG 69 *Tabes dorsalis*—Charcot joints (Case 91)

she been treated when the diagnosis of syphilis was first made. Except for persistent ataxia, symptomatic "cure" has been attained. Of interest is the syphilitic iritis appearing during regular and adequate treatment. Its response to arsphenamine was prompt.

**Case 91.** A seventy-two-year-old white man complained of pains in the legs. Five years before, following an injury to his left knee, it became swollen. During the following year he noted loose bodies in the joint, though he had little pain on walking. For four years he had had sharp, cutting momentary pains in lower thigh and leg, at times they were frequent in 12- to 24-hour periods. Similar pains occurred about the chest and trunk. In the two years before admission the leg became bowed, and the knee had felt as if there were sand in it. For a year there had been paresthesia of the right foot. A few months before admission he sprained the right ankle, and after this the right knee became "bowed" and

the knee "gritted" on walking. There had been pains in the right leg, like those of the left side.

Examination showed that the pupils were unequal, irregular, and reacted *very sluggishly to light but well during accommodation*. The ankle-jerks were absent, the knee jerks were obtained with reinforcement. Blood Wassermann and Kahn tests were negative. The spinal fluid was negative. The knees were enlarged, and crepitation on active and passive motion was present. Lateral mobility was increased. Roentgenograms showed joint destruction with much loose calcified material in the joint space.

**Comment.** This case represents bilateral Charcot joint of the knees in a patient with "burned-out" *tabes dorsalis* (Fig. 69).

**Case 92.** A thirty-two-year-old white auto salesman entered the Eye Clinic in April, 1935, because of failing vision. This began in the right eye several years before, and progressed to such degree that he was practically blind in this eye for the last year. About three weeks before admission he began to have diminishing vision in the left eye, so that he had to give up driving his car. For two years he had had attacks of epigastric pain and vomiting. He had a penile sore thirteen years before admission.

Examination revealed speech to be hesitant, slow, and slurred. Pupils were unequal, irregular, and fixed. Knee- and ankle-jerks were absent. Ophthalmoscopic examination showed white, atrophic disks. Only light could be distinguished with the right eye, only the largest newspaper headlines could be seen with the left eye. Vision was O D 10/0, O S 10/30. The visual field could not be obtained for the right eye, and was markedly constricted with the left. Blood Wassermann and Kahn tests were positive. Spinal fluid showed increased globulin 2 cells per cu mm, Wassermann test positive in 1.0 and 0.5 cc and negative in 0.2 cc, and a 4321100000 mastic test.

Intraspinal treatment with arsphenaminized serum was given every other week for six injections. (Dosage of serum was progressively increased from 5 to 14 cc.) After the fourth treatment the patient was able to read newspaper headlines and to see the landscape with his left eye. About fourteen weeks after the beginning of treatment he was again able to drive his car without trouble. At this time the left visual field had improved greatly. Vision was O D 4/1000, O S 8/200.

After intraspinal treatment was completed continuous treatment was given so that the patient received neoarsphenamine 0.6 Gm  $\times$  60, and bismuth  $\times$  86 in 152 weeks. In December, 1935, vision was O D 2/200, O S 15/200. In July, 1936, it was O D 5/200, O S 20/200, the left visual field was greatly improved, and the right could be charted for the first time. Blood tests were negative. In April, 1938, the spinal fluid showed normal globulin 4 cells per cu mm, a doubtful Wassermann test in 1.0 cc and negative in 0.5 and 0.2 cc, with a negative mastic test.

**Comment.** Progressive primary optic atrophy was stopped in this instance with definite subsequent improvement by the use of intraspinal treatment which was followed by continuous treatment.

**DIAGNOSIS.** Except for an occasional unusual case, *tabes dorsalis* is probably the easiest diagnosis which the general practitioner is called upon to make in the field of central-nervous-system disease. The history and the physical examination usually make the diagnosis, and it is but rarely that the spinal-fluid findings do not clinch the diagnosis. The Argyll-Robertson pupil with but rare exceptions (possibly in brain tumour and multiple sclerosis) means parenchymatous neurosyphilis—*tabes dorsalis* or paresis. Symptoms referred to the abdomen and due to visceral crises have led to many *uncalled-for laparotomies* which must be laid at the door of inadequate history taking and physical examination on the part of surgeons. A history of syphilis, Argyll-Robertson pupils, absent reflexes, and other attendant signs of *tabes dorsalis* should make the surgeon pause in the diagnosis of appendicitis, cholecystitis, and perforated peptic ulcer.

Peripheral neuritis, due to thiamin-chloride deficiency (formerly classified as alcoholic and diabetic neuritis), as well as lead and arsenic neuritis, may seem to simulate *tabes dorsalis* at times. There may be ataxia, weakness, loss of reflexes, and sensory disturbances, but the nerves are tender and there is muscular atrophy. The lack of Argyll-Robertson pupils and the absence of spinal-fluid abnormalities will settle the diagnosis.

Posterolateral sclerosis (combined sclerosis) may at times seem to simulate *tabes dorsalis* because of the posterior-column involvement. However, Argyll-Robertson pupils will be absent, and there will probably be neurologic signs of lateral-column involvement. *Achylia gastrica* and the demonstration of a hyperchromic macrocytic anemia (pernicious anaemia) would be helpful in the diagnosis.

I have seen pseudotabes twice in diabetic patients having had the disease many years. This is a rare condition.

The Charcot joint may appear in syringomyelia as well as in *tabes dorsalis*. The question of the neuropathic joint may come up in the case of syphilitic hydrarthrosis (Case 74), but the absence of the neurologic signs of *tabes dorsalis*, the examination of the joint, and the roentgenogram will establish the diagnosis. Hypertrophic arthritis may at times cause confusion in the diagnosis, and even the roentgenologic examination may not be too certain in its differentiation. However, the absence of a history of syphilis and the signs of *tabes dorsalis*, as well as blood and serologic studies, will satisfactorily rule out the probability of Charcot joint.

Optic atrophy may be due to brain tumour, retrobulbar neuritis, multiple sclerosis, and primary anaemia. Syphilitic optic atrophy may occur without the usual symptoms and signs of *tabes dorsalis*. Under such circumstances the general practitioner may have to ask for consultation with the ophthalmologist or neurologist.

**PROGNOSIS** Untreated tabes dorsalis may take one of two courses. The minority of cases become quiescent without any further progression. In addition there are the cases in which the spinal fluid becomes negative and are spoken of as "burned out" (Lightning pains and the like may persist). More often, however, tabes dorsalis is a disease progressing over a period of many years, with increasing disability, invalidism, and even death. Optic atrophy goes on to permanent visual impairment and practically always to complete blindness. The ataxia progresses so that the patient must use two canes or crutches to get about and finally must take to a wheel chair or the bed. A Charcot joint may disable the patient. Pylonephritis, as an ascending infection from cystitis resulting from urinary retention, may be the cause of death. Gastric crises and lightning pain may be disabling.

With treatment the physician hopes to control the symptoms and to stop the progress of the disease. Obviously, repair or restoration of nervous tissues already destroyed is not to be expected. Very early, possibly in the initial stage, before any destruction has occurred, one may see improvement and complete relief of certain symptoms such as lightning pains, bladder disturbance, ataxia, and impotence. However, when the process has become established with tissue loss, cure is not even to be considered. Often the disease progresses in spite of treatment.

O Leary reviewed the results of treatment in tabes dorsalis as found in the Co-operative Clinical Group material. Not only did he cover in detail the effect of treatment in general, but also the effect of the several forms of treatment which may be employed. His is probably the best paper for detailed information.

He shows that the effect of treatment on the blood tests is not of especial significance. However, he feels that the type of spinal fluid found in a tabetic patient at the onset of treatment has great prognostic importance. In the Type I group he found that 31 per cent were clinically arrested, of the Type II group 23 per cent were clinically arrested, and 11 per cent showed progression. Of cases with Type III fluids, only 19 per cent were arrested clinically and 19 per cent progressed. Of especial importance to the general practitioner and health officer is the finding that the milder grades of spinal fluid change became reversed, and clinical improvement occurred, by the use of only the simpler treatment methods. Thus here the physician can hope to accomplish a great deal with trivalent arsenic and bismuth. He may have to call upon the specialist in therapy in the case of patients with Type III fluids, as well as in those having certain clinical manifestations such as optic atrophy. O Leary warns that reversal of a positive spinal fluid does not necessarily mean arrest of the clinical process. He points out that one-fifth of tabetics with spontaneously negative spinal

fluids had clinical progression, and that in one-tenth of those becoming negative under treatment, progression occurred. The prognosis was found good in 28 per cent of patients in whom the spinal fluid was unstable, i e, fluctuating back and forth from positive to negative. Clinical progression occurred most often in patients with resistant spinal fluid. In one-fourth of such instances, clinical progression took place in contrast to a similar course in only one-tenth of those with spinal-fluid reversal.

He feels that the best clinical results are obtained in tabetic patients with symptoms of recent appearance and with syphilis of no more than ten years' duration. Briefly, results of treatment were as follows. Charcot joints and perforating ulcers were arrested in about half the cases. Ataxia disappeared in 15 per cent and improved in 41 per cent, and though results were good with all treatment methods they were possibly best with intraspinal treatment. Lightning pains were eradicated in 31 per cent and lessened in 35 per cent, and here, fortunately for the practitioner, it was shown that treatment with trivalent arsenic and bismuth gave the highest percentage of good results. Gastric crises disappeared in 44 per cent. Fever therapy by the use of malaria was the most successful form of treatment for crises. Diplopia disappeared in 83 per cent of instances, usually under routine (trivalent arsenic) therapy. Thus, except for optic atrophy, the routine therapy available to the average practitioner is very often successful.

Moore and his associates present the best evaluation of treatment in primary optic atrophy. They point out that if untreated this condition eventually progresses to blindness. It was found that from the onset of symptoms, blindness occurs within a year in 32 per cent, within two years in over 50 per cent, within four years in over 75 per cent, and that an occasional case may go as long as seven years. In Moore's study, visual acuity of 10/200 or less is rated as blindness, and success in treatment included (1) the prevention of blindness beyond the seventh year, and (2) if the lesion was unilateral, the sparing of the other eye from the disease process. The results of these observers indicated that antisyphilitic treatment of irregular and small amount had no effect upon the course of optic atrophy. Therapy with trivalent arsenic, generally adequate for syphilis, was found to delay blindness and to arrest the disease only occasionally. Intraspinal treatment seemed to arrest the process in about half the cases. Malaria therapy led to arrest in about 85 per cent of cases so treated.

General paresis (dementia paralytica, general paralysis of the insane) is the other common form of parenchymatous neurosyphilis. As in *tabes dorsalis*, this presents itself as a late manifestation of syphilis, usually making itself apparent in the second or third decade after infection.

Untreated it is a disease that is progressive, leading to death within a few years in practically all instances

**FREQUENCY** It is estimated by several authors that about 5 per cent of untreated syphilitic patients will develop general paresis. What factors may operate in addition to syphilis in causing the disease is unknown. It is usually pointed out that though syphilis may be present in primitive peoples, general paresis does not occur in such a population, and thus it is presumed to be a disease of civilized peoples. I am not sure that this can be accepted without question. It is possible that mental disease, supposed to be due to supernatural forces, may not be brought to the attention of medical missionaries caring for the less civilized peoples as are organic diseases. Some statistics seem to indicate that the incidence of general paresis is greater among the "white-collar" workers than in labourers, and greater in the white than in the coloured race. Males are more often affected than females, in a proportion of about five to one. Since the disease is manifested from 10-20 years after infection, the greatest number of cases fall into an age group of from 35-50 years. Various surveys have shown that from 5-15 per cent of the inmates of the institutions for the insane in this country have paresis.

In the Vanderbilt University Hospital Syphilis Clinic, among the 528 cases of central nervous-system syphilis, there were 69 cases of general paresis in addition to the 11 cases of taboparesis mentioned in the discussion of tabes dorsalis. (This does not include the cases admitted to the medical wards for treatment, and then sent back to private physicians or other treatment agencies.) The distribution as to race and sex was as follows: 41 white males, 5 white females, 14 coloured males, and 9 coloured females. Though the proportion of Negro to white clinic admissions is 2:1, the proportion in general paresis was 1:2.

**PATHOLOGY** The pathologic process in general paresis is that of a meningo-encephalitis. Grossly, the brain in advanced cases is smaller than normal due to cerebral atrophy. This is shown by a loss of volume of the gyri and widening and deepening of the sulci. With the loss of brain substance there occurs external and internal hydrocephalus. Cut section of the brain shows a loss of gray matter. The pia mater is often gray white in colour, cloudy, thickened, and may be adherent to the underlying cortex.

*Microscopically, the pathologic process in general paresis is both degenerative and inflammatory. The latter is characterized by vascular and perivascular inflammation characteristic of the syphilitic process. Inflammatory foci are also demonstrable within the brain substance, and here with suitable technic may be found the *T. pallidum*. Gliosis is general. The pathologic changes so characteristic in the cortex may invade the basal ganglia, brain stem, cerebellum, and there may be the associated*

changes of tabes dorsalis (taboparesis) The meninges show the changes described in meningovascular syphilis The above composite pathologic picture is thus one of a meningo-encephalitis

**SYMPTOMS AND SIGNS** Since a full psychiatric discussion of general paresis is out of place here, only enough of the clinical picture will be included to assist the practitioner in arriving at the probable diagnosis In the great majority of cases the attending physician will have to call upon a consultant both in establishing the diagnosis and in carrying out the therapeutic management For the clientele of the average physician and health officer such special consultation and treatment will probably mean commitment to a public institution for mental diseases

The disease may manifest itself first in one of several ways Usually, however, some mental aberration is the first abnormality noted by relatives, friends, or employer At times such disturbances as difficulty in writing, motor paresis or paralysis, or convulsive seizures may bring the patient to the physician The onset of the disease may be insidious, with slow progress, or may be more explosive, appearing as a definite psychosis

THE MENTAL SYMPTOMS are often classified under three headings

(1) *Mild Symptoms* Under this heading are grouped the early symptoms encountered in the slowly progressing disease Usually these are spoken of as changes in personality Irritability, outbursts of temper, inability to concentrate, and slovenliness of the person or dress may become apparent in persons previously not showing such characteristics Insomnia, anxiety states, headache, and ease of fatigue may offer reasons for consulting a physician Loss of weight is often marked Lack of judgment in a formerly astute businessman may be striking With progression of the disease, loss of memory becomes prominent There is a lowering of ethical and moral standards Loss of the ability to make simple calculations appears

(2) *Psychosis* Psychotic manifestations may be the first inkling of trouble in some cases In others, the milder symptoms progress to a psychosis The patient may become euphoric, and feel on top of the world Delusions of grandeur may develop, with boasts of power, wealth, and strength The physician is often promised great sums of money, cars, etc Volubility and incoherence in speech develop Disorientation may occur The psychotic symptoms may take the form of manic outbursts with hallucinations and delirium Again the manifestations may be of the depressive type, and suicide may be attempted Paranoid ideas may develop

(3) *Simple Dementia* Progressive mental deterioration takes place until finally the patient leads a vegetative existence He is disoriented as to time and place The patient must be fed, incontinence of urine and feces



develops, he becomes emaciated. Death usually occurs within three or four years of the onset, due to inanition, pneumonia, ascending-urinary-tract infection, or tuberculosis.

Epileptiform seizures are common. The convulsions may be of the jacksonian or focal type, or may be generalized (Case 94). Death may take place during such a seizure. They may be frequent for a period of time, to be followed by some remission in intensity and frequency.

THE PHYSICAL SIGNS are quite characteristic, and are essential in diagnosis. It is well for the general practitioner to remember that mild mental abnormalities, with little on physical examination, may be the first sign of this serious disease. The presence of the following signs should demand further study in a case which otherwise might be lightly dismissed. Pupillary changes commonly are present consisting of inequality and irregularity. They may be contracted or dilated. The Argyll-Robertson pupil is frequent, though often the reaction to light is sluggish rather than absent. Later in the course of the disease the pupils may become fixed to light and accommodation. Paralysis of the extra-ocular muscles may occur. If taboparesis is present, optic atrophy may be found.

A fine tremor of the facial muscles is commonly noted, in the eyelids, the tongue, and about the lips. The latter may be noted especially during speech. The facial expression may be described as vacuous. Speech is slurred and tremulous, and may suggest that of a drunken man. Test-phrases are often used to bring out this characteristic. Such are "Methodist Episcopal," "around the rugged rock the ragged rascal ran," "electricity," and the like. Repetition of such phrases several times results in accentuation of the speech difficulty. The fingers show a tremor, and the handwriting is tremulous. With involvement of the motor cortex hyperactivity of the deep reflexes may be present and the Babinski test may be positive. Hemiplegia or hemiparesis may be present.

If taboparesis is present, the findings described under tabes may be demonstrable in addition to those of the parietic state (Case 87).

LABORATORY FINDINGS. In the untreated patient suffering from general paresis, the blood tests for syphilis are positive in almost all instances. The spinal-fluid examination in the untreated patient will reveal a Type III change. At times the cells are as few as 20-30 per cu mm, and again as high as 150-250 per cu mm. Globulin is increased. The Wassermann test in the spinal fluid is strongly positive, that is, positive in all dilutions, and the colloidal curve falls into the first zone or parietic type. It is best to accept the viewpoint that untreated general paresis is never accompanied by a negative spinal fluid. If this statement is accepted, the physician will not make the error of diagnosing general paresis in the patient with

latent syphilis who may be suffering from a manic-depressive psychosis, or one with mental disease based on cerebral arteriosclerosis

**Case 93** A forty-year-old white man gave a history of a penile sore" fifteen years before. His blood test was found positive and he was given twelve weekly injections of neoarsphenamine. The lesion healed after the third injection, and his physician pronounced him cured because his blood was negative. Eight years later, after some malaise and dizziness, he developed right hemiplegia, which confined him to bed for two months. A lump remained in the right leg. At this time he received twelve injections each of mercury and bismuth, and six of neoarsphenamine. Treatment was stopped because of exfoliative dermatitis and jaundice. During the following six years the patient received courses of bismuth and mercury intramuscularly, and mercury by mouth. His blood test always was positive.

Some three months before being referred to us, he had to give up his work because of nervousness which had progressed for some years, memory loss for recent events, tinnitus, and difficulty in speaking. His wife added that he was irritable, inattentive, and did not seem to comprehend matters as in the past.

Examination showed the speech to be slurred. Pupils were unequal, and the right did not react to light. A slight right facial weakness was present. The deep reflexes in the lower extremities were absent. The Babinski reflex was present on the right. Blood Wassermann and Kahn tests were positive. Spinal fluid showed increased globulin, cells 750 per cu mm, Wassermann positive in 1.0, 0.5, 0.2 cc, and a colloidal mastic test of 5554321000.

The patient received ten treatments in the Kettering hypertherm, in each of which his temperature was kept at 105.5° F for at least five hours. After this course, the spinal fluid showed increased globulin, cells 12 per cu mm, Wassermann positive in 1.0, 0.5, and 0.2 cc, and a colloidal mastic test of 4332100000. Four injections of tryparsamide were followed by visual complaints, so they were stopped. In the next thirteen months, he received bismuth  $\times 34$ , and mercury in oil  $\times 20$ . Iodides were given at intervals. Blood Wassermann and Kahn tests became negative. The spinal fluid had improved in that the mastic test became negative.

At this time the patient's wife stated that he was becoming worse with respect to interest in family and home, and with greater loss of memory. He was inoculated with tertian malaria, and was allowed to have 12 paroxysms with fever of from 104°-106° F. He developed secondary anaemia and was debilitated so that convalescence was prolonged. He was given bismuth  $\times 10$ . His condition remained stationary, and antisypilitic treatment was stopped. At fifteen months after malaria therapy, the spinal fluid showed increased globulin, cells 1 per cu mm, Wassermann test doubtful in 1 cc. and negative in 0.5 and 0.2 cc, and a negative mastic test.

He received bismuth  $\times 12$ , two months' rest, and bismuth  $\times 12$ . Ten months after the last spinal fluid examination, this was repeated and found to be negative in all respects. Improvement had set in and the patient was doing some work as

a tinsmith, putting gutters on roofs. This improvement has persisted for three years and he is working for the first time in some years.

**Comment.** Here the treatment of early taboparesis was made difficult because arsenic could not be used in any form. Though repeated fever therapy is usually valueless, this case is an exception. Progression of the disease was stopped, and improvement followed a second course of fever treatment. It has also been shown that something can be accomplished by fever and heavy metal treatment alone. A vascular lesion caused hemiplegia some years before the appearance of the mental symptoms.

**Case 94** A forty two year-old white linotype operator was admitted to the hospital because of mental symptoms. Since the patient was irrational the history was obtained from the wife and father. He worked steadily until three months before admission, when work was discontinued for a time because of irritability. At home minor incidents "upset him," and caused outbursts of temper. One month before admission he had several transient attacks of right facial paralysis during which time he could not swallow or speak and the right side of the face would be rigid. Muscles in the extremities were not involved. One attack was followed by numbness in the right hand which interfered with his work. Two weeks before admission the patient's wife noted he would answer a question only after it had been repeated three or four times. About twelve hours later he had a severe convulsive seizure which lasted twenty minutes and was followed by unconsciousness for thirty minutes more. The following day he tried to work but could not because of weakness, nausea, and vomiting. Again he had a convulsive seizure as on the previous day, the onset being definitely right-sided. He was stuporous for a few days and then again became able to walk. He had been drinking quite heavily for six years and had had one convulsive seizure some years previously after a heavy drinking bout. (It was said that five years before admission he had some "pimples" on his penis which were diagnosed as syphilis, and that he was given "13 arm shots".) He stopped treatment and two weeks later developed visual disturbance with diplopia. This progressed for five months when he again consulted his physician who gave him thirteen more injections, some intravenously and some intramuscularly. After five of the intravenous injections the vision was again normal.)

Examination revealed an irrational, euphoric, and incoherent patient. His speech was slurred, and at times he was aphasic. The tongue was tremulous and deviated to the right. There was anaesthesia of the lower side of the right face. Deep reflexes on the right were slightly less active than on the left. There was a loss of pain and temperature sense over the right side of the body, with impairment to touch. Blood Wassermann and Kahn tests were positive. Spinal fluid study showed increased globulin, cells 50 per cu mm, Wassermann test positive in all dilutions, and a colloidal test of 4432100000.

He was successfully inoculated with tertian malaria blood, and allowed to have 12 paroxysms with an average temperature of 105° at the height of the fever. The patient became rational and memory improved. He received neoarsphenamine 0.6 Gm.  $\times$  3. Spinal fluid then showed increased globulin, cells

9 per cu mm, Wassermann test positive in 1 cc and negative in 0.5 and 0.2 cc, with a flat colloidal curve

Neoarsphenamine 0.6 Gm  $\times$  25, tryparsamide 3.0 Gm  $\times$  7, and bismuth  $\times$  23 were given, at the end of which the spinal fluid was completely negative. Blood Wassermann and Kahn tests were still positive. Tryparsamide had to be discontinued because of visual symptoms. Within several months after malaria therapy, the patient resumed linotyping, getting out an eight-page weekly newspaper free of errors. He received additional neoarsphenamine 0.6 Gm  $\times$  27, and bismuth  $\times$  22. His condition was satisfactory 3.5 years after fever treatment, and he was working steadily when last seen.

**Comment.** If the penile lesions represented acute syphilis, five years before the onset of mental symptoms, this is an unusually short interval for the onset of paresis. Clinically the patient had paresis. In addition there were manifestations of meningovascular syphilis. Improvement was very rapid under treatment, and recovery was complete except for residual slurred speech and facial tremor upon speaking.

**DIAGNOSIS** General paresis must be differentiated from diffuse meningovascular syphilis. The latter is more likely to have focal symptoms and signs, a fixed rather than Argyll-Robertson pupil, and will appear relatively soon after infection is acquired. Treatment is more successful in the patient with meningovascular disease, and this may be of assistance in diagnosis.

The milder or earlier symptoms of general paresis may suggest an anxiety neurosis or neurasthenia. The presence of any of the physical signs of general paresis demands further study of the spinal fluid, blood and more careful psychiatric evaluation. Often valuable information may be obtained from members of the patient's family.

In nonsyphilitic conditions which must be differentiated from general paresis, the laboratory data will be of great assistance. Consultation with a neuropsychiatrist may be necessary. Cerebral arteriosclerosis, senile dementia, and frontal-lobe tumours may closely simulate paresis. Chronic alcoholism at times is confused with general paresis. Each of these conditions may be differentiated from general paresis on the basis of negative spinal-fluid findings, aside from detailed psychiatric evaluations. Manic-depressive psychosis may be differentiated on the history, absence of physical signs of general paresis, and absence of laboratory data indicating the presence of neurosyphilis. It must be recognized, however, that nonsyphilitic psychoses may occur in patients having asymptomatic neurosyphilis (positive spinal fluid). The diagnosis in such instances must be made on clinical grounds.

**PROGNOSIS** Spontaneous remission in general paresis is so rare that if it occurs there is great question as to the accuracy of the diagnosis. Diffuse meningovascular syphilis may simulate paresis and may improve sponta-

neously For all practical purposes it may be said that untreated general paresis always will progress to simple dementia and death in from two to four years from the onset of symptoms

With treatment the outlook is not so gloomy (Cases 93 and 94) The results of treatment are generally classified in the psychiatric literature as follows (1) Complete remission is that state in which, following treatment, the patient is able to assume his previous place in society (2) Partial remission, or improvement, allows the patient to live outside an institution at home, or to hold a position at a lower economic level than previously (3) No improvement or progression means that confinement in an institution is necessary

With modern methods of treatment, essentially the use of fever therapy, one will find in the figures published from various institutions for the mentally ill such figures as follows complete remissions in from 25-50 per cent of cases, partial remission in from 15-40 per cent, and lack of improvement in from 10-25 per cent Obviously to obtain such relatively good results, cases must be properly selected The apparent variations in results published from various institutions no doubt reflect the degree of conservation shown in the selection of cases for treatment

O'Leary and a number of collaborators recently published an evaluation of fever therapy in general paresis Material from a dozen or so institutions was pooled for this evaluation, and included 1,100 cases treated with malaria and 320 treated with artificial fever From this study it is obvious that the earlier patients are treated after the onset of symptoms the better If the reader will remember the classification of patients into three groups on the basis of symptoms, (1) mild, (2) psychotic, and (3) deteriorated, the results shown in this study of 1,420 cases will be appreciated A clinical remission was obtained in 50 per cent of the mild cases, 25 per cent in the psychotic group, and 1-10 per cent of the deteriorated cases The chance of relapse after a complete remission was found to be only about 20 per cent Of the seventeen relapses in this study, fifteen occurred within three years of the remission Blood and spinal fluid reversals were twice as frequent with follow-up arsenic therapy after fever treatment as in those receiving no therapy subsequent to fever In about one-half of the cases with good clinical results, the blood and spinal fluids were not completely reversed

### RARE FORMS OF NEUROSYPHILIS

The various forms of neurosyphilis which have been considered are those which are relatively frequent. There remain a few other forms which are rarely encountered

## GUMMA

A gumma may develop in the central nervous system as in other tissues of the body. Gummata vary in size from very small ones to those of 2 or 3 cm. in diameter, and may be multiple or single. Small multiple gummata are found most often along the course of blood vessels. These give rise to the picture of vascular neurosyphilis, that is, obliteration of blood vessels. However, the large solitary lesions are for all intents and purposes tumours, and thus may produce the clinical picture of brain tumour. In a syphilitic patient presenting disease suggestive of brain tumour, gumma must be considered.

## MENINGOMYELITIS

Occasionally within the first decade of the syphilitic infection involvement of the spinal cord or its coverings may produce symptoms. This process may be patchy or diffuse, with involvement only of the meninges covering the cord or only of the substance of the cord, but usually both. The spinal roots may be affected, and endarteritis may be present in vessels of the spinal cord. Localized gumma formation may occur. From this pathologic description it is obvious that the clinical picture may be extremely variable. Posterior root involvement might lead to pain at varying sites. Anterior root involvement may account for flaccidity or atrophy. Sensory disturbances may occur.

As in other forms of myelitis the clinical picture varies. The paralysis may be flaccid or spastic, there may be paraplegia, hemiplegia, and the like. Anterior poliomyelitis may be simulated. Bladder, rectal, and sexual disturbances may be present. Posterolateral sclerosis may appear to be the diagnosis. The picture may be that of the chronic spasticity of Erb with involvement in the distribution of the brachial plexus. Pseudotabes is a tabetic syndrome appearing in a person with syphilis of only a few years' duration, sudden in onset, and due to meningomyelitis. These forms will need to be differentiated from a number of nonsyphilitic neurologic conditions. (Four instances of apparent syphilitic meningomyelitis have appeared in the Vanderbilt University Hospital Syphilis Clinic among the 528 cases of neurosyphilis.)

## HYPERTROPHIC MENINGITIS (PACHYMENINGITIS)

This may occur in the cervical region. Such a process involves all layers of the meninges. Due to dense granulation tissue and fibrosis, the meninges become thickened, tough, and exert such pressure upon the cord as to lead to underlying degeneration. Paralysis and atrophy of muscles of the upper extremity are characteristic.

## SYPHILITIC NEURITIS

This may be chronic, characterized by pains, as in tabes dorsalis, but without the clinical picture of tabes. It may persist for years, and paralysis may occur.

## TREATMENT OF NEUROSYPHILIS

*Reasons for Individualization*

Probably in no field of antisyphilitic treatment is individualization so imperative as in neurosyphilis. There are several reasons for this. Circumstances may contraindicate the method of choice, and another course may need to be followed. Neurosyphilis may not respond to one regimen, and a new attack may be necessary. Unexpected success may occur with simple methods of treatment making it unnecessary to carry out a more ambitious plan of treatment. From this it is apparent that the physician treating neurosyphilis must be prepared at any time to change a projected plan of treatment.

Before entering upon a discussion of the treatment of the various phases of neurosyphilis, two things should be emphasized. First it is essential that knowledge of the patient's physical status be as complete as possible. Many patients with clinical neurosyphilis, because of its late onset, fall into an age group in which some of the degenerative diseases have begun. For certain treatment methods, especially fever therapy, contraindications may exist in the form of nonsyphilitic heart disease, renal disease, arteriosclerosis, and the like. Secondly, the attending physician cannot rationally undertake any treatment scheme for neurosyphilis unless he understands well the type of central nervous-system disease with which he is dealing, and what its prognosis is.

Though the expressed intention of this volume is to provide a guide for the management of syphilis by the general practitioner or health officer, practical considerations make it necessary that certain warnings and advice be given relative to the treatment of neurosyphilis.

In Chapter 1, I indicated that the practitioner, if he is conscientious, should be able to manage the course of treatment in most patients with syphilis. However, in the field of neurosyphilis consultation with specialists may be imperative. If the physician will study his patient carefully and do repeated spinal fluid examinations, he may assume the treatment of asymptomatic neurosyphilis, meningovascular syphilis, and (to a certain extent) tabes dorsalis. But in the patient with general paresis, and in the tabetic patient whose disease is progressing while under treatment, who fails to improve, or who has optic atrophy, the attending physician should not assume responsibility for the type of treatment to be used. He may

usual cases of early syphilis in which the spinal fluid is negative. Since multiple spinal fluid examinations often will not be done for practical reasons, few of the mildly abnormal fluids will be found, and practically all will have been reversed by the time lumbar puncture is carried out toward the end of treatment for early syphilis.

**Type II spinal fluids** are the most common ones encountered in the routine spinal fluid examinations in apparently latent cases. *The treatment here must be continuous, and consist of relatively longer courses of arsenic and less heavy metal than in latent syphilis.* Furthermore nearsphenamine must be used in full dosage, 0.6 Gm. at least, unless the patient is a small individual. The course of arsenical treatment should consist of at least 10-12 weekly injections with courses of six weekly injections of bismuth intervening. Iodides by mouth are indicated. In late cases, treatment should be introduced by three weekly doses of bismuth to prevent possible Herxheimer reactions. After 8-10 months continuous treatment, spinal fluid re-examination should be carried out. If the titer of the Wassermann test has been reduced as well as the cell count, treatment should be continued during the second year for such improvement will usually continue. However, if no reduction in complement fixation titer has occurred, tryparsamide (3.0 Gm.) should be used in courses of 12-16 weekly injections with intervening bismuth courses of six weekly injections in a scheme of continuous treatment. Spinal fluid examination again will be necessary at 8-10 months. By such methods practically all cases (90-95 per cent, Moore) will show reversal of the spinal fluid. Usually this involves two to three years of treatment. It is our custom to give in the year following the conclusion of continuous treatment, two three-month courses of bismuth and iodides with alternating three-month rest periods.

If the above treatment does not reverse the spinal fluid, fever therapy may be indicated. Our choice for this additional therapy is based on circumstances somewhat as follows. If resistance to treatment is met with in asymptomatic neurosyphilis (Type II fluid) in infections of recent duration (of only several years) or if the patient is young, we are inclined to use fever therapy before giving up treatment. However, in an older patient, and especially in one who has had syphilis for 15-20 years without any manifestations of neurosyphilis in the past (such as cranial nerve palsies or hemiplegia), we are not so eager to use such additional treatment. With such problems and the question of fever therapy for consideration I believe consultation with a specialist in the field would be wise. Many of our patients with Type II spinal fluids come to us because of Wassermann fastness after a year or two of treatment elsewhere. In such cases tryparsamide is used at once. However, in selected patients, especially



those having been infected but relatively recently (several years) and in young patients, fever treatment may be used before tryparsamide.

**Type III Spinal Fluids** Patients with a Type III spinal fluid have a more serious prognosis, and present a more difficult problem with regard to obtaining serologic reversal in the spinal fluid. Moore advises fever treatment at once. Though our results cannot be presented now, we believe that not infrequently spinal fluid reversal occurs under intensive continuous routine treatment in these cases. Therefore our plan at Vanderbilt University Hospital is as follows. The continuous treatment plan outlined for the Type II spinal fluid cases is carried out for 8-10 months. If spinal fluid examination reveals a reduction in the titer of the Wassermann test, eventual success may be expected (cell count and a flattening of the colloidal curve are almost always obtained), and treatment is continued as in the Type II spinal fluid cases. However, if after the first 8-10 months reduction in titer is *not* obtained, a change in therapy is indicated. Our plan is to use fever in young persons and those with fairly recent infections, unless other disease contraindicates such treatment. If the patient falls into the older age group, or if the infection has been of 15-20 years' duration we are inclined to use tryparsamide as in the plan outlined for patients with Type II fluids. Spinal fluid examinations are carried out at 8-10 month intervals, and treatment is continued for a year after a negative spinal fluid is obtained unless no reversal has occurred by the end of three years. Treatment will rarely be completed under 2½-3 years. Two courses of 12 weekly injections of bismuth alternating with three-month rest periods are given during the year subsequent to the completion of continuous treatment. If fever treatment has been used, it is followed by tryparsamide and bismuth in continuous treatment as in the above plan. Iodides should be used at intervals throughout treatment in these plans of treatment. We must be prepared for failure even if all methods at hand are used. Case 95 illustrates this.

**Case 95** A thirty year-old white man was admitted to the clinic because of a penile lesion which was diagnosed as chancroid. Ten years before he had a penile lesion, and two years later was found to have a positive blood test and was given thirty intravenous injections.

Examination, except for the chancroidal ulcer, was negative. Blood Wassermann and Kahn tests were negative. Spinal fluid showed increased globulin, cells 40 per cu. mm., Wassermann test positive in 1:0, 0.5, 0.2 cc., and a mastic curve of 3210000000.

He was given arsphenamine 0.3-0.4 Gm  $\times$  19, and bismuth  $\times$  16, irregularly. Spinal fluid then showed increased globulin, cells 13 per cu. mm., Wassermann test positive in all dilutions, and a negative mastic test. Blood Wassermann and Kahn tests were positive.

The patient was inoculated with tertian malaria and was permitted to have 18 paroxysms with a fever of 103.5-106° F. In the subsequent four years he received neoarsphenamine 0.6 Gm  $\times$  21, bismuth  $\times$  50, and tryparsamide 3.0 Gm  $\times$  25. At times treatment was very irregular. During this time the spinal fluid was examined five times, other than a drop in cells, no change appeared, the Wassermann remaining positive in all dilutions. Blood Wassermann and Kahn tests were negative during the last two years of treatment.

**Comment.** Since this patient with asymptomatic neurosyphilis was irregular in treatment, malaria therapy was used early. "Wassermann fastness" in the spinal fluid persisted in spite of much treatment.

#### MENINGOVASCULAR SYPHILIS

In early syphilitic meningitis and neurorecurrence, the treatment is the same as for acute syphilis. Worthy of emphasis, however, is the use of full dosage of neoarsphenamine injections at four- to five-day intervals for the first three or four doses, prolonged courses of arsenic iodides by mouth, and accompanying injections of bismuth. Water-soluble bismuth will give a higher concentration of bismuth and may be valuable in the early stages of the disease. In these forms of neurosyphilis Herxheimer reactions need not be feared. Clinically, improvement is usually prompt. Subsequently, much as in asymptomatic neurosyphilis, continuous routine treatment, consisting of long arsenic courses and intervening bismuth courses of four, and later six, weekly injections, is carried out for a year. If reversal of the spinal-fluid Wassermann has occurred, treatment is carried out for another year. If the spinal-fluid Wassermann has not reversed, tryparsamide should be used in long courses with intervening bismuth. After 8-10 months of this, if the spinal fluid is still positive, fever therapy is indicated, to be followed by a year of tryparsamide and bismuth therapy. Thus treatment will be continuous for two to three years.

In the cases having more chronic meningeal manifestations, such as epilepsy, cranial-nerve palsies, and the like, it may be best to divide the responsibility for treatment with the neurologist or internist. Though some authors feel there is little danger of a Herxheimer reaction, such reactions have occurred in our experience. It seems wise to prepare the patient with iodides and three to four weekly doses of bismuth. Following this, treatment should be of the continuous intensive routine type. From the clinical viewpoint, improvement is usually satisfactory. If at the end of 10-12 months' treatment the spinal fluid is still positive, the patient's subsequent management should be somewhat along the scheme for the treatment of asymptomatic neurosyphilis, the choice of tryparsamide and fever therapy being dependent upon the state of the spinal fluid, the age and status of the patient, and the duration of the infection.

In late vascular neurosyphilis, the danger of a Herxheimer reaction is

prominent because an endarteritic process may be aggravated by the injection of arsenic. Therefore weekly injections of bismuth should be used for four weeks before arsenic is used. Iodides should be given in large doses. In young patients neoarsphenamine may then be used and a continuous plan of treatment should be carried out, as outlined for asymptomatic neurosyphilis. Often, however, vascular lesions occur in older persons. Under such circumstances treatment must be much more conservative with the use of smaller doses of neoarsphenamine. If vascular lesions are a part of general paresis, the treatment must be for the latter condition. In vascular syphilis it may be wisest for the practitioner to call upon a consultant both for diagnosis and treatment.

Optic-nerve or eighth-nerve involvement demands the advice of the specialist with regard to treatment, since fever therapy is almost certain to be immediately necessary.

#### TABES DORSALIS

The management of this form of neurosyphilis especially demands individualization in therapy. Some syphilologists believe it is wiser not to institute antisyphilitic treatment in "burnt-out" cases because of a possibility of lighting up the process. If, however, there are manifestations of late syphilis other than those of tabes dorsalis, some conservative treatment is indicated.

In the majority of cases the symptoms and signs and spinal fluid findings indicate an active and often progressing process, and treatment is therefore imperative. As was noted earlier in the chapter, O'Leary showed that most of the manifestations may be expected to respond favourably to routine therapy in a high percentage of cases. This is fortunate, for the practitioner has the opportunity to undertake at least the first part of the treatment in tabes dorsalis. However, it seems best that the attending physician should divide the responsibility of treatment by consultation with a specialist in the field of neurosyphilis.

Routine treatment should be continuous and intensive. It should be introduced by three to four weekly injections of bismuth in oil. Potassium iodide should be given. Then neoarsphenamine in full dosage (0.6 Gm except in small individuals) should be given at weekly intervals in courses of at least eight to ten injections. Between these courses bismuth should be used weekly in courses of six to eight injections. Spinal-fluid re-examination is carried out in eight to ten months. If symptomatic improvement has occurred, and if the spinal fluid changes have reversed, such treatment should be continued over two to three years' time.

If symptoms have not improved, or if the spinal fluid has not changed radically, other forms of treatment should be used. O'Leary says,

*"If during the first year of treatment of tabes dorsalis, or after 20 injections of arsphenamine and heavy metal, the spinal fluid is still positive, supplemental treatments should be employed"* (The italics are O'Leary's) Tryparsamide is the next form of treatment to be tried, given in long courses alternating with bismuth courses. If improvement occurs, well and good. On the other hand, if symptoms are not relieved, or if the disease is progressing, fever therapy or intraspinal therapy will be indicated, unless contraindications to either of these methods exist. These special forms of treatment may be indicated even before tryparsamide is given a trial, especially in cases showing progression, or in instances of treatment resistance, from a symptomatic viewpoint. Because of the relatively high incidence of optic-nerve involvement in tabes dorsalis, the use of tryparsamide is associated with the danger of aggravating this lesion. In view of danger in the use of tryparsamide, and the necessity of a decision relative to the use of intraspinal or fever therapy, the attending physician had best consult a neurologist or internist experienced in such therapy. This should be done before unsuccessful treatment is extended beyond the first eight to ten months of intensive routine treatment.

*Primary optic atrophy in tabes dorsalis demands immediate consultation with an ophthalmologist, and a neurologist or internist experienced in syphilotherapy.* The use of fever therapy at once is imperative in an attempt to stop the progress of the process. If contraindications to fever treatment exist, intraspinal or intracisternal injections of arsphenaminized serum are a second choice. Moore and his collaborators feel there is a certain danger of sudden blindness with the latter method of treatment in a small percentage of cases. O'Leary believes that a like danger exists in the use of malaria in optic atrophy, but Moore's experience does not bear this out.

Gastric crises may cause the patient much trouble. Codeine may be necessary. Morphine must be avoided because of possible addiction in a condition characterized by chronicity. In some patients amidopyrine is effective, along with sedatives. Other than special forms of treatment, there may be nothing left in severe cases except an operation to sever the pathways either in the spinal cord or in the roots. The management of the patient with a Charcot joint may require the assistance of an orthopedist. In the case of the "cord bladder" the urologist may help in the care of the patient. Amidopyrine may be very effective in lightning pains.

#### GENERAL PARESIS

When the diagnosis of general paresis has been established, the management should be in hands other than those of the general practitioner. The treatment of this condition is a problem demanding hospitalization, either in the general hospital, in the psychopathic hospital, or in an institution.

for the insane. No delay should be permitted until fever therapy can be instituted. Fever is followed by prolonged treatment with tryparsamide and bismuth. If contraindications to fever treatment exist, tryparsamide is the second choice of treatment.

In answer to questions so frequently asked with respect to the comparative efficiency of malaria and artificial hyperpyrexia, one can only point out that the study by O Leary and his collaborators, and of Ewalt and Ebaugh indicate in general that the results of both methods are about equal. In recent years, it has appeared that artificial fever therapy is gaining in popularity among those physicians who treat much neurosyphilis.

Finally, it should be emphasized again that in neurosyphilis so much is at stake that its management requires that repeated spinal fluid studies be done, that consultation with specialists be obtained, and that varied special methods of treatment be employed.

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## XIII

### SYPHILIS AND PREGNANCY

#### ITS RELATIONSHIP TO PREVENTIVE MEDICINE

FROM the viewpoint of preventive medicine, syphilis in the pregnant woman stands next in importance to acute syphilis. The publicity which syphilis has received in recent years has made itself felt in this field since the frequency with which blood tests are done in pregnant women has increased enormously. Such testing is exceedingly common in the prenatal clinics. Though it must be admitted that many private practitioners have not kept abreast of modern practice in this respect, many obstetricians are using serologic tests in their private patients as regularly as uranalysis and blood-pressure readings. Unfortunately, the family physician still all too often has the attitude that to do a test for syphilis in a woman whom he has known all his life—yes, may even have delivered—is an insult to her and to her family. However, the present generation is often ahead of the physician, and young women now are insisting on such examinations even over the expressed opposition of their physicians.

#### FREQUENCY OF EXAMINATION

In 1936 the American Social Hygiene Association made a study to determine the frequency with which pregnant women were examined for syphilis. Questionnaires were sent to prenatal clinics in all parts of the country. Replies were received from 268 clinics. In 250 of these (93 per cent), blood tests were part of the routine examination, whereas in the remaining eighteen clinics blood was drawn for testing if it seemed indicated. Serologic examination for syphilis had been carried out in 219,659 antepartum cases in these clinics. Of interest is the fact that the adoption of routine blood testing in many of the clinics had occurred only within the preceding two years. No doubt much additional progress has been made in the six years since this study. In the same study, questionnaires also were mailed to 250 physicians, all specialists in obstetrics. Of eighty-two replies, forty-two indicated that blood tests for syphilis were part of the routine antepartum examination. Some of these men had been following such a plan for a decade or more. The physicians averaged over one thousand patients each. Worthy of emphasis, as a matter of reassurance to the general practitioner, is the fact that these obstetricians feel that such an examination is feasible among private patients.

The combination of syphilis and pregnancy is of interest from two

viewpoints. One is the effect of pregnancy upon the syphilis, the other is the effect of syphilis upon the pregnancy. Though the former is not so interesting from a public-health viewpoint, it is of much interest as regards the biology of the syphilitic infection.

### THE EFFECT OF PREGNANCY ON SYPHILIS

Though in some syphilis clinics the number of females approximates that of males, cardiovascular and neurosyphilis are found three to five times more frequently in males than in females. Moore found twice as many positive spinal fluids in late syphilis in women who had not been pregnant after infection as in those who had. Solomon noted the high incidence of sterility in neurosyphilitic women in that 44 per cent had never been pregnant, indicating that these women had lacked the beneficial effect of pregnancy. Beck and Daily found that the Co-operative Clinical Group material indicated that pregnancy influenced the outcome in latent syphilis, as shown in Table XLI.

TABLE XLI

THE FAVOURABLE INFLUENCE OF PREGNANCY UPON THE RESULTS OF  
TREATMENT RESULTS IN SYPHILIS

	Number of Cases	Per Cent Satisfactory Treatment Results	Per Cent "Wassermann Fastness"
Pregnant . . .	283	42.4	18.4
Nonpregnant . . .	303	29.7	42.2

Some students of syphilis have felt that pregnancy may be indicated in syphilitic women as a therapeutic measure.

If pregnancy apparently influences the subsequent course of syphilis, a practical question having diagnostic and public-health implications comes to mind: what, if any, is the effect of pregnancy on the acute manifestations of syphilis? May pregnancy so alter the immune reaction of the host to the *T. pallidum* that acute lesions may be suppressed and infection go unrecognized? There is some evidence indicating that this is true.

Brown and Pearce showed twenty years ago that in the experimental animal pregnancy altered the course of infection. A tissue emulsion containing *T. pallida* was inoculated into eight pregnant rabbits and eight controls. In the latter group local lesions with lymphadenitis occurred within three to four weeks. Among the eight pregnant rabbits, four showed no clinical evidence of infection; three had slight infiltration at the site of inoculation without any lymphadenopathy, and only one

animal showed a lesion comparable to the control group, but the appearance of this lesion was delayed to the period of lactation. More recently various studies have shown that there may be a relationship between the severity of the manifestations of acute syphilis and the sex hormones (See Chapter 11)

In addition to this experimental evidence, clinicians feel that syphilis, acquired at about the time of conception may be profoundly modified in its acute course. It is believed that chancres are seen less frequently in infection during pregnancy, and that secondary manifestations may be much milder than in the nonpregnant female. Though this may be true, it should be noted that primary lesions may be more exaggerated at times, especially if they appear fairly late in pregnancy. Because of the increased vascularity of the external genitalia, chancres may be associated at times with massive edema of labia, with ulcers varying in size from 2-4 cm. in diameter. Due to the edema and excess secretion, the integument may be eroded and fissures develop between the thighs and labia majora. Bleeding from chancres, in making darkfield preparations, may be rather marked. Such lesions may show little of the induration associated with characteristic primary lesions. Not uncommonly there are multiple lesions.

### THE EFFECT OF SYPHILIS ON PREGNANCY

Though the course of syphilis in a woman may be rendered mild by pregnancy, the reverse is not true. Unfortunately, syphilis is highly deleterious to the offspring, causing either miscarriage, stillbirth, or the birth of a syphilitic child in a high percentage of instances in which no treatment is given.

It is now accepted as a fact that if a child has congenital syphilis, the mother has syphilis, even though her blood tests are negative. Infection of the fetus must take place from showers of organisms in the mother's blood stream. The placenta becomes infected, and, in turn, the child. It is commonly accepted that fetal infection takes place no earlier than about the middle of pregnancy (McCord, in a study of fetuses, has never found *treponemata* in any weighing less than 100 Gm., which is the weight at the end of the fourth month). From studies of the frequency of abortions in syphilitic and nonsyphilitic women, it seems that this complication occurs no more often in the syphilitic woman during the first trimester of pregnancy.

The duration of the infection in the mother possibly influences the severity of the infection of the fetus, accounting for stillbirth on the one hand, a surviving child on the other. If infection has occurred recently, either before conception or early in pregnancy, the fetus is almost certain to be infected. In such instances stillbirth at the fifth or sixth month is the



usual thing With greater intervals from the time of infection to pregnancy, the results will be variable It is commonly accepted that most babies, born at term from mothers who have had infection of few years' duration, are likely to develop manifestations of syphilis corresponding to the secondary stage of acquired syphilis If the mother has late syphilis the child is more likely to escape the acute manifestations, and to develop, in subsequent years, the symptoms and signs of congenital syphilis corresponding to tertiary lesions of acquired syphilis Furthermore, a woman with late latent syphilis may give birth to a syphilitic child after the birth of a normal child in an untreated previous pregnancy

If the mother is infected late in pregnancy, the child may escape infection, though there remains the possibility that the child may acquire syphilis in passing down the birth canal (Cases have been reported in which the normal child has acquired infection from a chancre or condylomata lata on the mother's vulva) Infection may occur so late in pregnancy that birth occurs before the organisms are widespread in the mother Case 96 offers such an example

**Case 96** A sixteen year-old unmarried Negress was admitted to the Obstetrical Clinic on November 17, 1938 Blood Wassermann and Kahn tests were negative She was delivered of a viable full term child on January 12th There were no lesions of acute syphilis, though Wassermann and Kahn tests were positive at this time She was admitted to the Syphilis Clinic on March 2, 1939 Examination showed circinate syphilids about the mouth, and papules on the palms

No clinical or serologic evidence of syphilis was found in the child on several examinations

The patient received arsphenamine 0.3 Gm  $\times$  27, and bismuth  $\times$  30 in fifty five weeks Seroreversal occurred within sixty days of beginning treatment, spinal fluid was negative in the tenth month of treatment

A second pregnancy began in April, 1940, and during it the patient received neoarsphenamine 0.45 Gm  $\times$  14, and bismuth  $\times$  14 in thirty six weeks She was seronegative throughout this pregnancy and was delivered of a viable child on January 6, 1941 There was no clinical or serologic evidence of syphilis in the child on several examinations The patient was placed on probation in February, 1941

In July, 1941, blood Wassermann and Kahn tests were positive Spinal fluid showed increased globulin, cells 10 per cu mm, Wassermann test positive in 1.0 and 0.5 cc., negative in 0.2 cc., and a negative mastoc test.

**Comment** Here syphilis was acquired sometime during the last eight weeks of the first pregnancy, since the blood tests were negative on November 17th and positive at delivery Secondary lesions were present three weeks later Of further interest is the fact that active infection was persistent since she developed a neurorecurrence thirty months later in spite of adequate treatment A second

pregnancy during the intervening time, though treated irregularly, resulted in a healthy child. The child was thus given protection even though neurorecurrence occurred in the mother.

Case 97 offers, by contrast, an example indicating that infection acquired earlier in pregnancy leads to infection of the fetus.

**Case 97.** A sixteen-year-old unmarried Negress was admitted to Obstetrical Clinic on October 26, 1939, having missed two menstrual periods. Blood Wassermann and Kahn tests were negative.

On April 25, 1940, it was noted that she had palmar papules. Wassermann and Kahn tests were positive. In the Syphilis Clinic it was learned that in October, 1939, she had seen a "scabbed sore" on the penis of her only sexual partner, and father of her child. In February, 1940, the patient developed a small genital lesion lasting two days. The palmar lesions appeared early in April.

Examination revealed a generalized lymphadenopathy, and a heavy seeding of papules on the palms and soles.

She received mapharsen 06×2, and bismuth×2, one injection of each being given at a five-day interval. She was delivered of a full-term child seven days after the last treatment, on May 15, 1940. Continuous treatment was given following the puerperium.

The child was found to be negative clinically and serologically on June 29th. When it was seen next, on August 6th, Wassermann and Kahn tests were positive; subsequent examinations verified this.

**Comment.** This patient developed the first evidence of syphilis at about the sixth month of pregnancy with frank secondary manifestations about a month before delivery. No treatment worthy of mention could be given, and the child had congenital syphilis.

Since examples of infection late in pregnancy and midpregnancy have been cited, it may be of interest to present an example of acute syphilis acquired some time before pregnancy.

**Case 98.** An eighteen-year old Negress, separated from her husband, was first seen in the Eye Clinic. About five months before, she noted a genital "sore" of a few days' duration. At the same time she had a nonitching rash of the trunk and extremities. (Her husband had a rash on his face at the same time.) Four months before admission the patient's eyes became "inflamed," and photophobia was marked. Though this gradually improved somewhat, her vision was described as if she were looking through a haze, and "spots swam" before her eyes.

Examination by the ophthalmologist showed the bilateral mild circumcorneal injection of iritis. The left cornea was slightly hazy. The left pupil was fixed to light and accommodation, and the right partially so, due to adhesions of the iris to the lens capsule as shown by the slit lamp. The right disk showed papilledema. Vision was O D 20/30 and O S 20/100. Blood Wassermann and

Kahn tests were positive. Spinal fluid examination showed increased globulin, cells 20 per cu mm, a negative Wassermann and mastic test.

In addition to iodides by mouth and atropine locally, she was given arsphenamine 0.3 Gm  $\times 4$ , and bismuth  $\times 4$ , the latter two drugs being given simultaneously. The iritis cleared up and vision improved.

Treatment was lapsed for six weeks because of nausea. In the following twenty-eight weeks neoarsphenamine 0.45-0.6  $\times 14$ , and bismuth  $\times 7$  were given. In the latter part of this period the patient became pregnant, and the dose of arsenic was increased to 0.6 Gm. At the end of the twenty-eight weeks she stated that following the last two injections of neoarsphenamine she had had epistaxis, bleeding from the gums, and had noted "red spots" in the eyes and on the tongue and lips. A test dose of neoarsphenamine of 0.45 Gm was given. Under observation, three hours later, petechiae began to appear in the conjunctiva, the mucosa of the mouth, palate, and lips. Arsenic therapy was stopped. Water soluble bismuth  $\times 8$  was then given bi weekly.

One year after her first visit to the clinic, she was delivered of a healthy child, later found to be seronegative and to have no evidence of syphilis. The patient's Wassermann test was negative, but the Kahn test was still positive. After the puerperium a vision of 20/30 was found in both eyes. A few posterior synechiae were still present in the right eye.

After the puerperium mapharsen was begun in doses of 0.1 and 0.2 Gm. Since no petechiae appeared, she was given 0.04 Gm  $\times 21$ , and bismuth  $\times 23$ , irregularly. Spinal fluid was negative. Both Wassermann and Kahn tests became negative and remained so for a known four years.

**Comment.** The patient had secondary syphilis, with two of the eye manifestations (iritis and optic neuritis), neurosyphilis, and became pregnant during treatment. The use of arsenic had to be discontinued due to purpuric manifestations. (The safety with which arsenoxide can be used in these cases was not known at the time.) In spite of inadequate treatment a nonsyphilitic child was obtained probably due to the fact that she received a total of thirteen injections of arsenic before and during the early part of pregnancy. Water soluble bismuth was used to maintain a higher bismuth level since we did not believe arsenic could be used in any form.

We have had families which have shown the natural course of untreated syphilis as related to pregnancy. The eldest one or two children have been normal. Then the disease has entered the family and a period of sterility of several years has occurred. This has been followed by several late miscarriages or stillbirths. Then one or two living syphilitic children have been born, and finally healthy children have been produced. Such examples are becoming fewer, because of more universal case finding and treatment of syphilis.

The question arises whether a time ever arrives when treatment is unnecessary in the pregnant syphilitic woman. It is probable that with many years of untreated infection, say 12-15 years, the chance of fetal

infection is much less than in the earlier years. However, women with syphilis of 15-20 years' duration have been known to give birth to syphilitic children. *Every pregnant woman must be treated!*

## DIAGNOSIS OF SYPHILIS IN THE PREGNANT WOMAN

The diagnosis of syphilis during pregnancy is almost entirely dependent upon positive serologic tests. In the presence of negative tests it may be made on the basis of history. A few patients will be found with the lesions of acute syphilis (Case 97). Usually, the diagnosis of syphilis must rest upon serologic tests since most pregnant women are seen in the stage of latency. Though all of our pregnancy cases are not available for analysis, 210 cases in Vanderbilt University Hospital Syphilis Clinic had the following distribution as related to the stage of syphilis (see Table XLII)

TABLE XLII

THE STAGE OF SYPHILIS AS FOUND IN 210 PREGNANT WOMEN

<i>Stage of Syphilis</i>	<i>Number of Cases</i>
Latent	159
Secondary	36
Secondary relapse	6
Central nervous system, asymptomatic	5
Primary	2
Late benign	1
Cardiovascular (aortic insufficiency)	1

*One must accept that a consistently strongly positive serologic reaction in pregnant women means syphilis.* However, it is also an incontrovertible fact that the pregnant woman with syphilis may have a negative blood test, thus giving a false sense of security when actually she is able to transmit the disease to the offspring. In a seronegative pregnant woman there may be a history of previous antisyphilitic treatment upon which the diagnosis of syphilis may be made. If, in the history of the seronegative woman, there is anything suggestive of acute syphilis, or if the history of pregnancy reveals either stillbirths or infant death shortly after birth, all possible collateral evidence of syphilis should be collected. Thus congenital syphilis in living children, or clinical or serologic evidence of the disease in the husband, may be of great assistance in the evaluation of the situation. Beck and Daily state that seronegativity occurs in about 10 per cent of syphilitic gestations.

Table XLIII, modified from one by Jeans and Cooke, may be of interest

with respect to the serologic reactions in parents of syphilitic children (Unfortunately for present-day comparisons, the test done was the less sensitive complement-fixation reaction only, since the figures were collected over a decade ago)

TABLE XLIII

DURATION OF INFECTION AND THE COMPLEMENT FIXATION REACTIONS IN THE PARENTS OF SYPHILITIC CHILDREN (MODIFIED AFTER JEANS AND COOKE)<sup>1</sup>

Parents	Number of Families	Strongly or Moderately Positive in	Weakly Positive	Negative
		Per Cent	Per Cent	Per Cent
Mothers				
children under 2 years	383	85.1	7.6	7.3
children over 2 years	264	68.9	6.9	24.2
Fathers	195	51.3	5.1	43.6

<sup>1</sup> I have grouped the authors' 'strongly and moderately positive groups together since with the more universally used flocculation tests this group would undoubtedly be reported as positive. The 'weakly positive group no doubt would show doubtful and some positive flocculation tests. In the negative group there also would be some doubtful and even positive reactions with the more sensitive tests.

Blood tests should be done upon the first prenatal visit. If this is negative before the fifth month, it should be repeated at about the seventh month, so that subsequent infection during pregnancy may be ascertained.

## PREVALENCE AND PROGNOSIS

Numerous statistical studies have been published indicating the frequency of syphilitic infection in pregnant women, the incidence of untoward effect upon the fetus or child, and the beneficial effect of anti-syphilitic treatment.

The frequency of syphilis in pregnant women will vary greatly with the economic levels from which the subjects are drawn. A rate as low as 0.3 per cent in 1,000 consecutive cases in the private practice of an obstetrician represents one extreme. Among those of a lower social scale, the frequency will be higher. One author found 4 per cent of 11,983 women, delivered at Bellevue Hospital in New York City, to have syphilis. Another, in an analysis of pregnant women in the Washington University Clinics in St. Louis, found syphilis in 3.3 per cent of 3,245 white women, and in 14.6 per cent of 1,455 coloured women.

The prognosis in the untreated pregnant woman may be measured in terms of the outcome of the pregnancy. Though many papers have appeared showing the serious results of untreated syphilis, nothing is to

be gained by summarizing more than a few of them. McKelvey and Turner found that untreated syphilis in pregnancy resulted in stillbirths in 45.9 per cent, and that 64.5 per cent of the living children were syphilitic. McCord reported that untreated syphilis in pregnancy accounted for 57.6 per cent of premature pregnancies and 87 per cent of late abortions in his material. Speiser found that 81.5 per cent of the offspring of untreated syphilitic pregnancies ended in deaths due to syphilis or in congenital syphilis. Cole reported that at Western Reserve University obstetrical service stillbirths occurred four times as often in syphilitic as in non-syphilitic women.

A consideration of the improved prognosis obtained by antisyphilitic treatment accentuates the seriousness of untreated syphilis in pregnancy. Improvement in prognosis varies with the amount of treatment received, and time in the pregnancy at which treatment was started.

The amount of treatment given prenatally is of great importance. Speiser reported that in his patients, syphilitic living babies were 12 times more frequent in the untreated than in the treated group of syphilitic pregnant women. Halloran found that among 264 women who received less than six doses of arsenic during pregnancy, 20 had abortion or stillbirths, 53 syphilitic infants, and 191 (72 per cent) nonsyphilitic children. Six to ten doses of arsenic were given during pregnancy in 119 women, and 80 per cent of these gave birth to living nonsyphilitic children. Among 84 women who received more than ten doses of arsenic, 93 per cent of the children were nonsyphilitic.

Soule concluded that if at least 10 injections each of arsenic and bismuth can be given the mother, the chances of a normal nonsyphilitic child being born are about 95 per cent. McKelvey and Turner reported no syphilitic offspring if from 12-15 injections of arsenic had been given before birth. The Co-operative Clinical Group studies showed that if at least ten and better fifteen injections of arsenic and a like amount of bismuth can be given starting early in pregnancy, the chances are that 91 per cent will end with the birth of nonsyphilitic infants.

It is important that treatment be started early in pregnancy. The Co-operative Clinical Group found that irrespective of the amount of treatment given, 78.4 per cent of those treated before, and 60.8 per cent of those treated after the fifth month gave birth to nonsyphilitic offspring. It is also found that even with less than ten injections of arsenic plus heavy metal, if treatment was begun before the fifth month of pregnancy, only 5 per cent of the offspring were syphilitic as compared to 20.7 per cent if such treatment were given after the fifth month. However, in answer to the frequent question as to whether anything is to be gained by treat

ment if the syphilitic woman presents herself late in pregnancy, the answer must be in the affirmative

The Co-operative Clinical Group figures show that 68 women with untreated early syphilis gave birth to nonsyphilitic children in only 34 per cent of instances, whereas of 66 women with early syphilis who had some treatment late in pregnancy, 49 per cent had normal infants. The Group also found that of 77 women with untreated late syphilis, 47 per cent had nonsyphilitic living children, of 152 in the same stage, but given some treatment after the fifth month, 66 per cent had normal children. It was also shown that in early untreated syphilis, miscarriage, abortion, or still-birth occurred in 46 per cent of pregnancies, if some treatment was given late in pregnancy this was reduced to 7.6 per cent. In Table XLIV, Ingraham, in a review of 386 pregnancies from the Philadelphia General Hospital, lists the outcome as related to time treatment was begun.

TABLE XLIV

TIME AT WHICH PREGNANT SYPHILITIC WOMEN REPORTED FOR TREATMENT  
COMPARED WITH EXPECTANCY FOR SYPHILIS IN THE OFFSPRING<sup>1</sup>

<i>Treatment Begun</i>	<i>Number</i>	<i>Approximate Percentage of Syphilitic Children</i>
Before pregnancy and continued to time of delivery	5	0
Between first and fourth months	67	5
During fifth month	62	35
During sixth month	86	35
During seventh month	48	50
During eighth month	59	70+
No prenatal treatment	59	80+
Total	386	

<sup>1</sup> Modified from Ven. Dis. Inform.

A question which bothers practitioners is whether treatment is necessary during pregnancy even though the mother has had adequate antisypilitic treatment in the past or has been treated through a previous pregnancy. In the state of our present knowledge this question can be answered only by the dogmatic statement that *every woman must be treated during each pregnancy*. (However, the Co-operative Clinical Group found no instances of syphilitic children born to women pregnant one to three years after infection if adequate treatment had been given. In addition, in fifty-two mothers pregnant after "cure," no instances of syphilis were found in children born up to fifteen years after infection.)

Other authors have felt that adequate treatment for acquired syphilis in the past may make the mother safe. However, reference to Chapter VIII

will remind the reader that adequate therapy does not insure the patient against infectious relapse. This fact, and the experience of many observers as well as our own, indicates that congenitally syphilitic offspring may be born of mothers who have had adequate treatment in the past. This may occur even though the blood tests are negative. In summary, the following quotation is taken from a U S Public Health Service publication "It becomes obligatory, therefore, to insist that every woman who has or has had syphilis must receive antisymphilitic treatment during every pregnancy, irrespective of the amount of treatment which she had had in the past, and irrespective of her apparent clinical status, provided she shows no evidence that she is intolerant to the treatment."

### PREGNANCY IN THE CONGENITALLY SYPHILITIC FEMALE

There is a small possibility of the mother suffering from congenital syphilis giving birth to a syphilitic child. A few such cases have been reported, though the frequency is certainly low. A safe rule to follow is to treat the mother, though it should not be drastic and should be individualized.

### MANAGEMENT OF THE PREGNANT WOMAN

The objective in the treatment of the pregnant woman will be discussed merely as related to the fetus, and not to the stage of the disease in the mother. The discussion on the prognosis in pregnancy, without and with treatment, amply substantiates the fact constantly emphasized to the medical profession, that antisymphilitic treatment of the pregnant woman is a most fertile field for preventive medicine. Premarital blood tests may provide the knowledge to the married couple of the presence of syphilis. The prevention of syphilitic offspring by adequate treatment is thus made possible.

The education of the public relative to prenatal examinations and follow-up is essential to the proper management of the syphilitic mother. Best results in diagnosis and treatment cannot be attained if the pregnant woman does not consult her physician until late in pregnancy, or if, in the event that she does consult him earlier, he does not obtain a blood sample for testing. By treatment of the pregnant syphilitic woman, the objective to be obtained is the birth of a nonsyphilitic child. (In addition, it is much easier to treat the mother than the syphilitic infant or child.)

The proper management of the pregnant woman with respect to syphilis should include the following considerations



1 Early diagnosis so that treatment may be adequate Blood should be drawn for tests for syphilis in the woman coming for prenatal examination as early as the first blood-pressure determination or uranalysis If this is negative in the early months of pregnancy, it should be repeated at the sixth or seventh month, since she may have acquired the disease at about the time of becoming pregnant or subsequent to the first test

2 If the diagnosis is made early enough to permit of adequate treatment, *this should consist of at least 15-20 injections of arsenic (neoarsphenamine 0.45-0.6 Gm, or arsenoxide 0.4-0.6 Gm) and some heavy metal* The last course of injections in pregnancy should consist of arsenic Since women often do not consult a physician until about the fourth month of pregnancy, there will remain about 20-22 weeks available for treatment before delivery Under such circumstances a plan somewhat as follows is used (a) the first course consists of eight weekly injections of arsenic, bismuth being given simultaneously with the first four injections of arsenic (the hazard of a Herxheimer reaction in a fairly young woman is outweighed by the benefit of arsenic to the child), (b) the second course consists of four to six weekly injections of bismuth, and (c) the last course consists of eight weekly injections of arsenic, and is continued to the time of delivery even though it may be two or three weeks beyond the calculated time

3 Every syphilitic woman should be treated no matter how late in pregnancy she appears for treatment If the plan as mentioned above cannot be carried out, variations may be used in an attempt to get at least ten injections of arsenic into the patient If, for example, as often happens in our clinic, a woman is sent to us only five or six weeks before the expected date of delivery, I have used the following plan (Arsenoxide or its derivatives, because of a greatly reduced toxicity, can be used more frequently than the arsphenamines) Mapharsen 0.4-0.6 Gm (or clorarsen 0.45-0.67 Gm), depending on the weight of the patient, is given every fourth day, with a simultaneous injection of bismuth every other time Thus in five to six weeks the patient may receive about ten injections of arsenic and five of bismuth With this scheme for a few weeks' treatment at one extreme, and the more ideal one at the other, schedules can be worked out for other periods available for treatment before the termination of pregnancy

4 If the syphilitic woman who is being treated with trivalent arsenic becomes pregnant, no alteration of the treatment plan is necessary because of the pregnancy This sometimes means several months' more treatment than might be necessary otherwise (If the woman becomes pregnant during treatment for neurosyphilis with tryparsamide, a change to trivalent arsenic is imperative)

5 Treatment should be given every pregnant woman known to be syphilitic, whether the blood is negative or positive, whether there has been previous treatment or not, and even though she has had normal children in previously untreated or treated pregnancies. This is accepted practice by such agencies as the Co-operative Clinical Group, the United States Public Health Service, and the like. Until more evidence is available to the contrary, it would seem wise for the reader to follow this practice.

6 In the woman diagnosed as syphilitic during pregnancy, the treatment is carried out for the benefit of the fetus. Subsequent to the termination of pregnancy, treatment may be modified to meet the requirements of the syphilitic status of the patient. The therapy of the various types of syphilis was discussed in previous chapters.

### CONTRAINDICATIONS TO TREATMENT

Only rarely is it impossible to carry out ideal treatment. The pregnant woman seems to stand arsenic therapy as well as the nonpregnant female. In our experience we have met with contraindications to the use of arsenic only a few times. These have been previous exfoliative dermatitis, syphilitic aortic insufficiency, and toxemias of pregnancy. In the first two we have depended upon heavy metal only in treatment. The latter we have treated not at all.

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## XIV

### CONGENITAL SYPHILIS

BY J CYRIL PETERSON, M D

CONGENITAL syphilis is to be distinguished from syphilis contracted at or after birth. It is an infection acquired during fetal life. The term "hereditary syphilis" is preferred by some authors because it emphasizes the transmission of the infection from the mother to the fetus. The use of the term hereditary is, however, more properly reserved for conditions transmitted through the germ plasm. No one now believes it possible for the father to transmit syphilis to his offspring without the intermediary infection of the mother, nor do we believe it possible for congenital syphilis to result from direct infection of the ovum. Colles observed, in 1837, that while syphilitic infants might infect their wet nurses, they never infected their mothers. This was variously misinterpreted until the development of adequate laboratory tests for syphilis. Now we know that the seemingly healthy mother is already infected.

#### INCIDENCE

The incidence of congenital syphilis varies markedly with various economic and social levels of society. There are no reliable statistical studies available on the general incidence of the disease. All clinic figures are unbalanced by the attempts to get patients of known syphilitic families in for study. Incidence studies based upon the rate of syphilis found in individuals upon admission into special groups are objectionable, in that they are not representative of the general population and often represent limited social or religious segments of the lower economic levels. This chaotic state is well reflected in the various findings quoted in Chapter XIII on maternal syphilis. From these figures it seems reasonable to assume that in most clinics the incidence of syphilis will be about 3 to 5 per cent in white mothers and about 10 to 15 per cent in coloured mothers.

Of the pregnancies occurring in untreated syphilitic women, it is probable that 80 per cent will be associated with fetal infection. About 30 per cent of these infected fetuses will die as a result of the infection before delivery. A high percentage of them will be prematurely delivered, though alive. Twenty five per cent of those delivered alive with syphilis will succumb because of the infection itself, the prematurity, or other factors, all most directly influenced by the fetal infection. This effect of syphilis on the fetus is summarized in Table XLV.

TABLE XLV

THE EFFECT OF SYPHILIS ON THE FETUS IN UNTREATED MATERNAL SYPHILIS<sup>1</sup>

Miscarriage and stillbirths	24%	
Born alive, free of syphilis	20%	
Born alive, with syphilis	56%	
Die in neonatal period		25%
Survived early syphilis, but may develop late manifestations		75%
Total	100%	

<sup>1</sup> Approximate percentages based on interpolations of figures from various sources

These figures allow one to make certain prognostications regarding the incidence of syphilis. If one assumes that 3 per cent of all women have syphilis, that syphilis is no bar to pregnancy, and that 40 per cent of the children infected survive, then  $4 \times 0.3 \times 100 = 12$  should approximate the percentage of children with syphilis found in the general population of clinic social levels in this country. This figure is nearly that observed in the few unselected population groups studied, but is only 30 per cent of the levels often observed in clinic populations.

One must not be too certain in ascribing syphilis in childhood to congenital infection. Acquired syphilis, while much less frequent in children than congenital syphilis, comprises 10 per cent of the cases of syphilis found in children at Vanderbilt University Hospital. Furthermore, the general application of good prenatal care will bring about better treatment of maternal syphilis, and will produce a decrease in congenital syphilis that may make acquired syphilis a relatively more frequent disease of childhood.

Fundamentally, the problems of congenital syphilis can be approached only by consideration of the problem of maternal syphilis, and, from a broader viewpoint, the problem of syphilis in the woman of child bearing age. It is quite certain that the present intensified attempts to control syphilis have in some localities succeeded in diminishing the occurrence of congenital syphilis, and that they will, if continued, soon lead to marked decrease in the incidence of congenital syphilis.

The education of the woman with syphilis should emphasize the absolute necessity of taking treatment with each pregnancy. It is doubtful that many women would jeopardize their unborn offspring if they were sufficiently informed. Certainly the physician should not be responsible for failure to treat the pregnant woman, as in Case 99.

**Case 99** A thirty year-old white woman contracted syphilis from her first husband. She was treated continuously for two years, and had had a persistently

negative Wassermann reaction. Her physician told her she should again receive treatment if she became pregnant. When she became pregnant she told her obstetrician of her syphilitic infection and her former physician's instructions. The obstetrician thought further treatment unnecessary. Her child appeared normal at birth, but at two months developed florid syphilis. The child made an uneventful recovery with treatment, but the family relationships were subjected to an unnecessary strain.

As has been stated in Chapter XIII, the treatment of all women with syphilis from the fourth month until the end of pregnancy will eliminate 90 per cent of fetal syphilis which would otherwise occur.

Inadequate treatment during pregnancy, even though it may not prevent fetal infection, will in many instances so modify the disease that miscarriage, stillbirth, or premature delivery may be prevented, and the child is more likely to be in a condition permitting subsequent successful treatment. This improvement in the viability of the infant is enough to demand treatment of the woman with syphilis no matter how late in pregnancy the infection may be discovered. The opportunity for even a single treatment is not to be neglected.

### SOURCE

Congenital syphilis invariably starts as a blood-stream invasion from the placenta, and the analogue of the primary phase of acquired syphilis is thus eliminated. The placenta becomes infected through the treponemal septicemia which the mother has in a secondary stage of syphilis, or from occasional showers of the organisms in the blood stream if her infection is latent.

The placenta shows certain characteristic lesions. There is usually diffuse enlargement of the placenta, with an increase in its weight in relation to the weight of the infant. Normally the placenta weighs 16 to 20 per cent of the infant's weight, but in syphilis the placenta may weigh 25 to 30 per cent of the infant's weight. There are numerous vascular lesions, chiefly an endarteritis, which lead to abnormalities in the chorionic villi. The villi show a diffuse increase in connective tissues with a marked decrease in the number of blood vessels present, and these connective tissues are edematous. These changes account for the increased placental weight. Often syphilis of the placenta remains focal in character and may be much more difficult to demonstrate.

Syphilis of the placenta is usually followed by syphilis of the fetus, but this is not an absolute certainty and it is conceivable that syphilis of the placenta can exist without penetration to the fetal side and consequent fetal infection. On the other hand, fetal infection often occurs when the placenta is not demonstrably infected.

**Variability.** When the treponema passes from the placenta to the fetus there may be a tremendous invasion of the tissues, so great that the treponemata may become as numerous as the tissue cells. Such an overwhelming infection results in death of the fetus, and though examination of the tissues may show relatively little gross derangement, microscopic study of specially stained sections will show the *T. pallidum*. The fetal invasion, on the other hand, may be minimal, and may require a variable incubation period before becoming manifest. In fact, it seems probable that a small percentage of infants may go through infancy and early childhood without ever showing any evidence of their infection. In these cases the diagnosis can be made only on the basis of the antibody response to the infection, the development of a positive Wassermann reaction.

This variability in the fetal infection is correlated with the activity of the syphilitic infection in the mother. With a recently acquired infection she is not only more likely to transmit the infection to her unborn child, but the infection in the child is likely to be more severe than if the mother's infection is of longer duration. A generalization of this is known as Kossowitz's law, which states, in effect: *fetal syphilis in succeeding pregnancies is less likely to be severe*. That time is not the only factor associated with this variation in the degree of infection transmitted to the offspring is shown by the fact that there may be relapses, and that fetal syphilis even in severe form may follow normal pregnancies in untreated mothers.

The observations which follow are based principally on the study of 550 children with syphilis observed in the Pediatric Clinic of Vanderbilt University Hospital.

### COURSE

Earlier, both here and in Chapter xiii, it has been pointed out that severe syphilitic infection of the fetus results in fetal death, and, therefore, in miscarriage, or in premature or mature stillbirth in approximately 25 per cent of all pregnancies in untreated syphilitic women. This statement needs no further elaboration.

In addition to fetal death a relatively high percentage of viable children of syphilitic mothers are born prematurely, and may die either as a result of their prematurity or of the associated syphilitic infection. In either instance this may occur without the child showing gross manifestations of the syphilitic infection.

Of these children there will be a very small percentage who have at birth, or develop in the first few days of life, findings of congenital syphilis. They may show skin lesions, particularly large bullae and indurated thickening of the skin of the face, often soon denuded and associated with

the discharge of serous or serosanguineous fluid. Some, though not all, of these infants may be emaciated, wizened infants at birth. They are the dried up "little old man" infants often described in text book pictures of congenital syphilis. Children with outstanding manifestations of syphilis at birth, or those who develop them in the first week, often do not survive even though the syphilis may be recognized and treated early. This state is illustrated by Case 100.

**Case 100** This was a three-week-old infant whose mother developed secondary syphilis late in pregnancy, and received only two or three treatments before delivery. The infant was said to have been full term, but its weight was estimated at four pounds. At one week the child began to snuffle, and a week later she developed "blisters over her hands and feet which soon broke and peeled." She had rubbed her eyebrows until they were bleeding. The child was edematous, pale, and showed a generalized maculopapular rash. The extremities were denuded by the rupture of large bullae, and there were excoriations and fissures about the mouth and nose. There was a serosanguineous nasal discharge with almost complete nasal blockage. The roentgenograms of the bones showed a severe osteochondritis. Treatment consisted of general supportive measures, intramuscular injections of sulfarsphenamine, and mercury rubs. Though there was no unfavourable reaction to the treatment, the child did not improve, began to have convulsions, and died five days after admission.

The children who survive the neonatal period may occasionally show poor development and malnutrition as a result of their syphilitic infection, but this is certainly not usual. The majority appear to be healthy normal children even when subjected to suspicious scrutiny. Almost all of these infants will, however, show definite clinical manifestations of syphilis if they are followed closely for a period of six months to a year. This efflorescence of the infection may be so minimal that it is difficult to detect, or it may be so violent as to carry the patient off in a very short time. Generally it can be expected that 25 per cent of the children born alive with syphilis will succumb during the first two years of life. This figure is now being lowered in many clinics as a result of earlier diagnosis and improved methods of treatment.

*The 75 per cent of syphilitic children who survive may do so as a result of treatment or a spontaneous decline in the activity of the syphilitic process. This progression into latency may occur early in the first year, or it may occur only after a remission and a relapse late in the second and occasionally even in the third year.*

Latency may be followed by the development of late manifestations. These manifestations are analogous to the tertiary stage of acquired syphilis. Late lesions usually appear between the third and fifteenth years, but we have seen a destructive lesion in the nose of an infant of ten months,

and we have seen interstitial keratitis developing in a girl over twenty years of age.

## MANIFESTATIONS

The clinical manifestations of congenital syphilis can be conveniently separated into three groups: those which are *early* manifestations, corresponding essentially to the type of lesion seen in secondary syphilis; *late* manifestations, corresponding to the lesions of tertiary syphilis; and *stigmata*, which are scars remaining from either the early or late lesions

### MANIFESTATIONS OF EARLY CONGENITAL SYPHILIS

Our material included 227 infants who were younger than two years of age when they were admitted to the clinic; 165 were younger than six months of age, twenty-four were six months to one year of age, and thirty-eight were one to two years of age.

**Hepatosplenomegaly.** Marked enlargement of the liver and spleen, usually found together, is the most frequent clinical finding in early congenital syphilis, and is present in 64 per cent of the infants seen for the first time during the first six months of life. This enlargement cannot be differentiated from that seen in infants in conjunction with many other infections except that enlargement is usually greater. The liver enlargement is due to the persistence, to an unusual degree, of fetal blood forming islands and a diffuse increase in connective tissues. The liver cells tend to be immature and imperfectly formed. Though there is often a slight icteric tint to the pallor seen in infants with syphilis, one very rarely encounters marked jaundice.

This diffuse cirrhotic involvement of the liver is in part responsible for the edema found in some patients with congenital syphilis. In these cases the hepatic insufficiency is associated with an inadequate protein metabolism and there is marked lowering of the serum protein, total protein levels of 4 Gm. or less with reversal of the albumin globulin ratio being not uncommon.

**Skin Lesions.** Involvement of the skin has in our experience been the second most frequent clinical finding of early congenital syphilis. Children when seen first at an age under six months show definite skin involvement in 52 per cent of the cases. The skin lesions may be of such variability that one should consider all skin lesions in infants, which cannot be positively identified, as being syphilitic until proven otherwise. Certain characteristics of syphilitic skin lesions are of help in differential diagnosis. They almost always involve the palms of the hands and soles of the feet, and they may be associated with desquamation in these areas. The maculopapular type of lesion is the most common variety. When the lesions occur about



the mouth and nose they are prone to become indurated, fissured, and to be associated with bloody weeping. Some of the commonly found skin lesions are illustrated in Cases 101, 102, and 103.

**Case 101.** A coloured infant was born in Vanderbilt University Hospital to a mother with untreated secondary syphilis at term. The blood Wassermann and



FIG. 70. Early congenital syphilis—maculopapular rash (Case 101).

Kahn were negative. At three weeks the child appeared to be normal. At six weeks she was found to have a generalized maculopapular rash, thin "moth-eaten" eyebrows, snuffles, hepatosplenomegaly, anaemia, hemoglobin 6.2 Gm., and osteochondritis. Figure 70 shows the type of skin rash present. The blood Wassermann and Kahn tests were negative. On treatment with acetarsone by mouth (increasing from 0.002 Gm. per lb. daily during the first week to 0.01 Gm. per lb. daily after three weeks), there was a disappearance of the skin lesions in less than two weeks. The patient lapsed treatment after eight weeks.



FIG. 71. Early congenital syphilis—papulopustular rash (Case 102).

**Case 102.** A six-week-old white female was brought to the clinic because of a rash of five days' duration. The mother and father knew that they had syphilis, but the mother was not treated during pregnancy. The only other pregnancy occurred five years before, and the child was normal. Examination showed a well-developed and nourished girl. She had two or three dozen raised reddish-brown lesions over her face and extremities, and a few macular syphilids on the metatarsal pads. One of the toes showed a paronychia. These lesions are

illustrated in Figures 71 and 72. There was no lymphadenitis, and the liver and spleen were not enlarged. The blood Wassermann and Kahn tests were positive. There was metaphyseal rarefaction and periostitis consistent with congenital syphilis. The spinal fluid was normal. On acetarsone by mouth (increasing from 0.002 Gm per lb daily during the first week to 0.01 Gm per lb daily after three



FIG. 72. Early congenital syphilis—papulopustular rash (Case 102)

weeks) the lesions disappeared in two weeks. The Wassermann and Kahn reactions were reversed after two courses of treatment (twenty weeks on acetarsone and eight weeks of mild mercurial-ointment rubs). Treatment was discontinued after fifty-six weeks. There was no relapse within one year after treatment.

**Case 103.** A coloured female aged five months was brought to the clinic because of a rash of one month's duration. Her sister, eight years old, was known to be syphilitic, but three children (six, four, and two years of age) were not syphilitic. The mother had had only five treatments seven years before. Examination showed a well-developed and nourished coloured girl. She had on her chin three annular syphilids, and the soles of her feet showed desquamation with slight redness (see Figs 73 and 74). There was a general glandular enlargement but no hepatosplenomegaly. The long bones were not examined. The blood Wassermann and Kahn tests were positive. On acetarsone by mouth (0.002 Gm per lb daily during the first week increasing to 0.01 Gm per lb daily after three weeks), the lesions disappeared in three weeks. Two courses of therapy (twenty weeks of acetarsone and eight weeks of mild mercurial ointment rubs) resulted in reversal of the blood Wassermann and Kahn tests. Treatment was stopped after four courses.

These illustrations show only a few of the many varieties of skin lesions encountered in early congenital syphilis. Typical condylomata lata may be seen occasionally in early infancy, but are usually seen after the first six months of life. They represent chiefly subacute or recurrent lesions. However, small, moist, slightly raised, perianal and vulval lesions are seen

Fig 73



Fig 74



FIG 73 Early congenital syphilis—circinate syphilid (Case 103)

FIG 74 Early congenital syphilis—plantar desquamation (Case 103)

very commonly along with other skin lesions in the infants less than six months of age.

Other ectodermal disturbances are seen frequently in infancy. The hair is often thin, and quite uneven in distribution. The eyebrows in particular are apt to be uneven. The nails may also be dystrophic, appearing to have been pinched into structures almost like claws, with paronychia frequently complicating the disturbance.

**Snuffles.** Syphilitic rhinitis as observed in our material was the third most common clinical manifestation of early congenital syphilis. Forty-nine per cent of our patients seen in the first six months showed this lesion. Careful observation would probably greatly increase the frequency with which rhinitis is found. Snuffles is the term commonly applied to the lesion, and suggests the obstruction which may be present, often so severe that it interferes with nursing. This obstructive phenomenon is usually out of proportion to the other evidence of inflammation. The discharge may be irritating, and may be associated with some excoriation of the nares or even nasal bleeding. These features tend to differentiate

this lesion from the rhinitis of ordinary upper-respiratory infections Snuffles is very frequently the first clinical manifestation of early syphilis Any nasal discharge in early infancy which persists for more than a few days, which is blood-tinged, which causes irritation of the nares or which causes obstruction with interference to nursing, should be regarded as highly suspicious of syphilitic infection

**Anaemia.** Extreme degrees of anaemia are so commonly found in early congenital syphilis that this feature should be interpreted as a part of the symptom complex The degree of anaemia is illustrated in Cases 101 and 105 where patients only a few weeks old and who had not been ill very long had hemoglobin levels of 6.2 and 8 Gm per 100 cc The anaemia presents no specific picture, and cannot be differentiated from anaemias due to other infection Forty per cent of our patients under six months showed this anaemia to a point where it was of definite clinical significance

**Edema.** Often in association with anaemia, but more particularly in association with marked changes in the liver, we have observed generalized edema In 18 per cent of our patients this was an outstanding finding Minimal edema was probably overlooked in many other patients Certainly many of the patients showed marked lowering of their serum proteins without evident edema All edematous patients, however, showed lowering of the proteins when the necessary studies were made In some of these patients there was evidence of kidney damage, a little albumin, and a few to many hyaline and granular casts in the urine This finding did not in most instances seem of a degree which would explain the edema

**Kidneys.** A review of our material, both clinical and pathologic, did not permit us to conclude that congenital syphilis is associated with any specific renal lesion We did find quite a number of instances in which there was a well-marked interstitial nephritis, but we also found several instances of acute hemorrhagic nephritis, particularly in small infants coming to postmortem examination with extensive skin lesions

**Meningitis.** Meningovascular lesions with or without symptoms of meningitis have been shown to occur in one-third or more of the infants with congenital syphilis Our early practice of doing lumbar punctures only when indicated makes it impossible to verify this figure from our material These patients may show bulging of the fontanel, stiffness of the neck, positive Kernig's sign, convulsions, and increasing hydrocephalus Symptoms are, however, present in only a half or less of those in whom characteristic spinal fluid changes may be demonstrated Examination of the spinal fluid shows a slight to moderate mononuclear pleocytosis, 15 to 200 cells, increased proteins, positive colloidal gold or mastic curves, and positive Wassermann or Kahn tests This form of meningitis, in contrast

to the lesions of the central nervous system in late congenital syphilis, requires no special consideration. Case 104 shows what may be expected of such a patient.

**Case 104.** A four-month-old white male was brought to the clinic because his head seemed too large, and because of difficulty in breathing. At three weeks he developed a generalized rash, and had difficulty in breathing. With this he



FIG 75 Early congenital syphilis—syphilitic meningitis (Case 104)

had a thin blood tinged discharge from his nose. The enlargement of his head was noted by his family three weeks before he was brought to the hospital. Examination revealed a mild hydrocephalus, head 16.5 inches in circumference, a slight opisthotonos, a tense fontanel, scanty irregular hair, no eyebrows, snuffles, general glandular enlargement, hepatosplenomegaly, osteochondritis, and periostitis. His general attitude is illustrated in Figure 75. Laboratory studies showed hemoglobin to be 9.0 Gm, spinal fluid 177 lymphocytes, Wassermann reaction positive in 1.0, 0.5, and 0.2 cc, Pandy reaction positive and colloidal gold sol curve 555543221, blood Wassermann and Kahn tests positive.

Following intramuscular injections of sulfarsphenamine (0.005 Gm per lb to 0.01 Gm per lb, after the first two doses) there was rapid improvement. The spinal fluid cell count dropped to twenty-eight after two treatments. The Wassermann reactions in the blood and spinal fluid were negative after twenty injections of sulfarsphenamine and eight weeks of mercury-ointment rubs. There was no relapse, and therapy was discontinued after forty injections of sulfarsphenamine, and sixteen weeks of mercury rubs. At this time there was no evidence of the previous hydrocephalic state.

**Osteochondritis.** The most commonly found lesion in early congenital syphilis is osteochondritis, demonstrable only by roentgenograms but so characteristic that it is of great diagnostic importance. Seventy-five per cent of the infants seen in our clinic for the first time during the first six months of life showed this lesion in a form demonstrable by roentgenograms.

The bones probably show in all cases, at some time, changes characteristic enough to be diagnostic. In the zone of greatest growth near the epiphysis, treponemata lodge, multiply, and produce an inflammatory reaction—connective tissue infiltration—which interferes with the growth of the bone. There results an increase in density and irregularity of the zone of provisional calcification, also a replacement of true bone by granu-



FIG 76 Early congenital syphilis—metaphyseal rarefaction (Case 105)

lation tissue. The bones growing with greatest rapidity show these changes to the greatest degree, chiefly the long bones (particularly the proximal end of the tibia and the distal ends of the ulna and radius). There is always a periostitis, reflecting in the area of active lateral growth a change similar to that seen at the ends of the long bones, but this may not be of a degree sufficient to permit demonstration by roentgenograms. Case 105 illustrates the osteochondritis.

**Case 105** The patient was a coloured male aged three weeks who was delivered at home at the end of a seven and a half months gestation. Of two previous pregnancies, one ended in the premature delivery of a child who died in two hours, and the second was terminated at seven months by a stillbirth. The mother had been found to have a positive Wassermann during pregnancy, but said she could not afford to attend the clinic for treatment. The child was brought to the clinic because it was not nursing well. Examination showed a 3½ lb infant, with slight desquamation of the palms and soles and palpable

glands in the cervical and inguinal areas. The child was anaemic, hemoglobin 8 Gm, but was not edematous. The blood Wassermann and Kahn tests were positive. Figure 76 shows the lesions found in the bones. The increased density in the zone of provisional calcification, the marked metaphyseal rarefaction, the irregularity in the ulnar epiphysis and the periostitis are characteristic enough to allow a diagnosis of congenital syphilis. The child was given small doses of sulfarsphenamine intramuscularly (0.005 Gm per lb of body weight) twice a week and made a prompt, satisfactory response to treatment.

When osteochondritis is severe there may be pathologic fractures in the area adjacent to the epiphysis. These fractures are often incomplete, are usually impacted, and are of no great clinical significance except for the fact that the pain results in inhibition of normal movements, pseudoparalysis, and that they may also be the seat of a superimposed secondary pyogenic osteomyelitis. Treatment of the syphilis and the pyogenic infection, if present, results in very rapid healing of both the fractures and the osteochondritis. The lesion tends to heal spontaneously even in the absence of treatment, and may disappear by the end of four to six months. Active osteochondritis is rarely seen in children older than eight months.

**Choroiditis.** Another lesion said to be seen in early congenital syphilis is involvement of the eye in the form of a choroiditis or less frequently as an iritis. Unless looked for carefully, those lesions may be overlooked, we have observed none in our material.

Only 6 per cent of the infants seen in our clinic during the first six months of life could be shown to have syphilis without manifest lesions. A few of these had histories suggestive of earlier lesions.

While most of the lesions seen in infants in the first six months of life may also be seen in children from six months to one year of age, lesions of any kind were found in only 50 per cent of our patients of the latter age group. Twenty-five per cent showed persistent skin lesions, a similar number showed snuffles, and 30 per cent showed bone or periosteal changes.

**Periostitis.** One of the more characteristic lesions found in the last half of the first year is the development of marked periostitis. The slowness of growth of bone from the periosteal membrane makes changes occurring in this zone appear at a later date than those appearing at the ends of the bone even though a similar process is involved in both lesions. Case 106, though younger than the patients showing the greatest changes, shows typical syphilitic periostitis persisting after the osteochondritic changes have almost completely healed.

**Case 106.** A white female of five and one-half months was admitted to the clinic for regulation of her feedings, and because of continued diarrhoea. She had been on an inadequate diet all her life, and appeared starved. She was the result

of the fourth pregnancy, the first two having ended in miscarriage at six to seven months and the third in the birth of a normal child. Examination showed pigmentation from a previous generalized dermatitis, marked emaciation and dehydration. Roentgenograms of the long bones showed marked periostitis (Figs 77 and 78).

The patient was started on intramuscular injections of sulfarsphenamine in

FIG 77

FIG 78



FIGS 77 78 Early congenital syphilis—periostitis (Case 106)

doses of 0.005 Gm per lb of body weight. There was fever following the injection, an increase in the diarrhoea and in spite of general supportive measures the patient expired. Postmortem examination showed an extensive ulcerative enterocolitis, in addition to the syphilitic bone changes.

**Dactylitis** Another bone lesion usually seen relatively late in early congenital syphilis is an osteitis of the phalanges, syphilitic dactylitis. This lesion must be differentiated from tuberculous dactylitis, sometimes an impossibility without roentgenograms. The typical tuberculous lesion shows a destructive process, and frequently breaks down to form a fistula, a complication not seen in syphilitic dactylitis.



**Case 107.** A fifteen month old white male was brought in because he would not use his left arm or right leg. His mother had received six injections for syphilis late in pregnancy. At three months he had had snuffles and a generalized dermatitis. He had a typical syphilitic dactylitis (Fig 79). Roentgenograms of the long bones showed no syphilitic lesions except the dactylitis. There were, however, lesions suggestive of scurvy to account for the pseudoparalysis. The

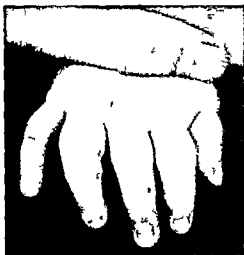


Fig 79 Early congenital syphilis—dactylitis (Case 107)

blood Wassermann and Kahn tests were positive. The spinal fluid was normal. After three treatments with sulfarsphenamine given in ten days' time, the patient was discharged to the clinic. He did not return for a year, and at that time the dactylitis had disappeared. Poor attendance necessitated treatment for seven years, and he finally completed four courses of treatment. His blood Wassermann and Kahn tests were negative after seven treatments given over a period of two years.

**Condyloma Latum** While condylomata were seen in 2 per cent of our cases younger than six months of age, usually in conjunction with other skin manifestations, they are more definitely a recurrent type of skin manifestation, and were seen in 13 per cent of our patients observed for the first time during the second year of life. These lesions are large, moist, poorly epithelialized warty growths usually found around the anus and vulva, but occurring occasionally at the angle of the mouth or between the digits. The demonstration of *T pallida* by darkfield examination of exudate from these lesions is usually accomplished with ease.

#### STIGMATA OF EARLY CONGENITAL SYPHILIS

Some of the lesions of early congenital syphilis characteristically produce scars which may persist into late life as stigmata of the infection.

**Facies** The severe involvement of the nose in a persistent case of rhinitis in infancy may result in subsequent facial distortion. This is seen most frequently as a result of syphilitic rhinitis. The long-continued infection may interfere with the growth of the nasal bones and the maxillae, resulting in a relative overgrowth of the frontal bones and the mandible.

FIG 80



FIG 81



FIGS 80-81 Facial distortion due to congenital syphilis (Case 108)

This gives the patient a saddle nose deformity and a syphilitic facies. This lesion is illustrated by Case 108.

**Case 108** An eight year-old white girl was brought to the clinic for syphilis of her eyes. She was born prematurely weighing 3 lb. at birth. In the first few days she was said to have had blisters of the palms and soles. This infection was not treated though the physician noted the lesions and questioned the father about the possibility of syphilitic infection. She survived infancy and aside from the usual childhood diseases she was well until three months before admission when she began to have redness of her right eye and photophobia. Soon the parents noted a dull skin over her eye. Three weeks before admission the left eye became similarly involved. She was then taken to the family physician who had blood tests done and gave her two injections of bismuth subsalicylate in oil.

Examination showed typical syphilitic facies (Figs 80 and 81) Hutchinson's teeth and in both eyes a deep-seated vascularization of the cornea with steamy infiltration to the point of marked interference with vision. Her blood Wassermann and Kahn tests were positive. Examination of the spinal fluid showed a positive Wassermann reaction with 1.0 cc., 0.5 cc. and a doubtful reaction with 0.2 cc. She was treated daily with intravenous injections of typhoid bacilli to

produce a fever of  $104^{\circ}$  to  $105^{\circ}$  F for a period of five days. During this time the pupils were dilated with atropine. At the end of a week there was marked improvement in her eyes, and she was discharged to continue treatment under her home town physician. Two months later her eyes showed complete healing of the keratitis with a residual network of empty blood vessels. She showed at this time, however, a loss of her pupillary reaction to light, and a larger pupil on the left. Because it was thought that these findings might indicate an active central nervous-system infection, her spinal fluid was re-examined and showed positive reactions in 1.0, 0.5, and 0.2 cc, but no increased cells, protein, or change in the colloidal gold sol curve. She was readmitted for malaria inoculation, and was allowed to have eight malarial chills. Following this and further treatment to complete two years of continuous alternating bismuth and neoarsphenamine therapy, the patient's spinal fluid is positive only in 1.0 cc. The eye signs were unchanged.

**Hutchinson's Teeth** The most commonly observed stigmata are the changes found in the permanent teeth. The tooth buds of the permanent incisors and the sixth-year molars are in the early formative stage during the first few weeks of life. An active syphilitic process in this period interferes with the nutrition of the teeth, and certain characteristic changes follow. The upper central incisors and less frequently the other incisors show at eruption, or shortly afterward, an imperfection of the enamel of the biting surface. The tooth soon becomes notched from erosion of this imperfect enamel. The dentine is also hypoplastic. The teeth are widely spaced, rounded, peg-shaped, and often present a screwdriver taper rather than a normal contour. Case 109 developed these dental changes.

**Case 109** A white girl aged six years was admitted to the clinic because of contact with tuberculosis. She was the result of the eleventh pregnancy with the immediately preceding six pregnancies terminating either as stillbirths or producing enfeebled infants who died in the first few days of life. Both parents had inadequately treated syphilis.

Examination of the patient revealed no signs of symptoms suggestive of syphilis, but the blood Wassermann and Kahn tests were repeatedly positive. After two courses of antisyphilitic treatment, 20 sulfarsphenamine and 8 bismuth injections, her Wassermann and Kahn tests were reversed. She was given 56 sulfarsphenamine and 16 bismuth injections during two years of clinic attendance. Photographs of her teeth two and a half years after treatment, at the age of 11 years, show typical Hutchinson's teeth (Fig. 82).

The molars show a lesion somewhat different than that found in the incisors. The base of the tooth is relatively normal, but the cusps are hypoplastic and poorly enamelled, giving the molar a pinched appearance. The changes in the molars occur more frequently than may be apparent, because these teeth are prone to early decay, and unless examined soon after eruption are often found to be merely carious shells.

**Rhagades** Another characteristic stigma of early congenital syphilis is the development of radiating linear scars about the mouth, and less frequently about the anus, when these areas are the seat of early fissured lesions. These scars are commonly called rhagades. They are relatively rare lesions, being seen in only 1 or 2 per cent of our cases.

**Choroiditis** Lesions of the choroid present in early syphilis may,



FIG. 82 Congenital syphilis—Hutchinson's teeth (Case 109)

in healing, leave characteristic scars which last throughout life. These are pale atrophic areas often bordered by pigmentation.

#### MANIFESTATIONS OF LATE CONGENITAL SYPHILIS

Sixty-one per cent of our patients seen after the first two years of life showed no active lesions of congenital syphilis. There are in our files records of 272 patients with congenital syphilis who were over two years of age when they were admitted to the clinic. This group may have included a few patients who had latent acquired syphilis, but in the great majority the infection was certainly of congenital origin.

**Interstitial Keratitis** Interstitial keratitis was the most frequent lesion of late active congenital syphilis. Twenty-two per cent of our patients older than two years had interstitial keratitis at the time they were first seen. This lesion is at first a mild episcleral vascularization followed by vascular infiltration of the deep layers of the cornea, nebulous exudation into the deep corneal structures, and, with these changes, moderate to severe photophobia. As the lesion progresses, the vascularization becomes more intense, and the hazy infiltration of the cornea becomes more opaque and more general in distribution. With the severe states there is apt to be iritis and iridocyclitis, though these lesions are frequently overlooked because the keratitis is so prominent. Both eyes are usually involved, though there may be weeks' and months' difference in the time of onset in the two eyes.

The lesions tend to run a course little influenced by the usual antisyphilitic therapy. Fever therapy may at times produce dramatic improvement, and will usually speed recovery. Untreated, the lesions become quiescent after many months. Severe lesions may heal without impairment of vision, but they often leave small leukomatous infiltrations which may obstruct vision. Following healing there is always an empty network of blood vessels which remains permanently as a stigma of the preceding activity. This stigma can be visualized only with magnification and oblique light, and does not impair the vision. The course of interstitial keratitis is illustrated in Case 108.

**Neurosyphilis** The second most common lesion of late congenital syphilis is, in our series and in the experience of others, involvement of the central nervous system. The true incidence of this lesion, as in the case of early meningitis, is not reflected in our studies because lumbar punctures were not routine before starting treatment until recent years. We have, however, found, as others have, that the coloured race escapes this lesion to a much greater degree than does the white. Two and seven tenths per cent of our coloured patients had demonstrable symptomatic involvement of their central nervous system, while 12.7 per cent of our white patients showed similar involvement.

Syphilis of the central nervous system has its origin in the general dispersion of the treponemata which occurs during the efflorescence of early syphilis. It has been observed that 30 per cent or more of infants will show the passage of the infection beyond the blood brain barrier as manifested by the finding of pleocytosis in the spinal fluid and positive spinal fluid Wassermann reactions. In a few this represents an overwhelming infection so that a higher percentage of such patients die in infancy. In general, there is almost the same level of central nervous-system involvement in late as in early congenital syphilis. There is little doubt that every child found to have late central nervous-system involvement had a positive spinal fluid from infancy to the time this manifestation appeared. This means that every child who has a positive spinal fluid Wassermann reaction is, even though he may at the time be normal, a candidate for the development of a hopeless disorder of the nervous system. Every child should have the benefit of a spinal fluid examination at the beginning of treatment. No child free of symptoms but with positive spinal fluid should be allowed to lapse therapy before the spinal fluid changes have reverted to normal.

The earlier lesions of the central nervous system are chiefly a meningo-vascular involvement. With the progression of the disease, these vascular lesions may result in focal or diffuse manifestations. There may be the gradual development of paralysis, hemiplegia, or even quadriplegia. Occa

sionally there may be sudden vascular accidents. About half of those who have these focal manifestations show evidence of general involvement of the cortex with marked mental deterioration. This is the result of a diffuse cortical sclerosis which follows the increase in the vascular involvement.

The various clinical manifestations of acquired neurosyphilis are found in children, but there is seldom clear-cut paresis or tabes. More frequently one sees overlapping patterns. Speech defects, loss of memory, fears, blindness, emotional instability and more obvious deterioration phenomena, such as loss of habits of cleanliness in children who appeared normal during their early years, are often presenting complaints. The two most common physical findings are hyperactive reflexes and pupillary changes, often the typical Argyll Robertson pupil, but also simple inequalities in size. The spinal fluid Wassermann reaction is invariably positive in these cases. There is also an increased number of cells, usually from 15 to 300 mononuclears per cubic millimeter, an increase in protein, and changes in the colloidal gold sol curve. Case 108 illustrates asymptomatic neurosyphilis.

**Bone Changes.** Involvement of the bones and joints is the third most common manifestation of late congenital syphilis. Eight per cent of our patients older than two years showed bone changes in some form. Clutton's joint, a painless hydrarthrosis usually involving the knee, is seen most frequently. This often starts as a unilateral involvement, soon involving both knees. Untreated, the course of the lesion may fluctuate for months or years before final complete healing. Under antisyphilitic therapy, healing usually occurs in a few weeks. The other bone lesions seen are persistent hypertrophic periostitis, osteitis, and gummata, most frequently involving the tibia. These manifestations are quite comparable to similar lesions occurring in acquired syphilis.

**Gummata.** Gummata occurring in the soft palate and nasopharynx were the next most common lesions in our material. These lesions occurred in 3 per cent of our late cases. A child with a gumma of the nasal septum represents the only late case in which we were willing to make a diagnosis of syphilis without associated positive Wassermann and Kahn tests. That patient was thought by several consultants to have syphilis, and her lesion which had been present for many months healed promptly on antisyphilitic therapy. Gummata about the nose and pharynx are prone to break down, and to produce perforations of the soft palate or the nasal septum, depending upon the localizations of the process. Gummata may also occur in the bones of the extremities, particularly the tibia, and less frequently the skull. Gummata occurring in other soft tissues, including the viscera, are in congenital syphilis so rare as to be pathologic curiosities.

**Blindness** Optic atrophy occurs only in conjunction with a more general neurologic involvement which may be either manifest or asymptomatic.

**Deafness** Involvement of the auditory apparatus in contrast to optic neuritis occurs quite independent of any evidence of general neurosyphilis. The lesion is thought to be due primarily to a labyrinthitis. The loss of hearing for high tones is quite common, while deafness for conversation is relatively rare.

#### STIGMATA OF LATE CONGENITAL SYPHILIS

As has been mentioned, interstitial keratitis on healing may leave leukomatous scars, which are no different than the scars from other parenchymatous keratitis. However, the network of empty blood vessels which remains is a recognizable syphilitic scar.

Gummata of the nasopharynx may upon healing leave perforations of the soft palate and of the nasal septum which are quite characteristic.

Optic atrophy and nerve deafness may exist as stigmata of earlier active involvement of the central nervous system and the labyrinth, respectively.

The hypertrophic osteitis of the tibia may, even after treatment, leave the shin bowed anteriorly in the deformity commonly known as the saber shin.

### DIAGNOSIS

#### DIAGNOSIS OF EARLY CONGENITAL SYPHILIS

The diagnosis of early congenital syphilis in its florid states is not difficult. The varied association of snuffles, rashes, hepatosplenomegaly, general debility, anaemia, edema, etc., presents a picture which to the initiated is easily recognized. When one has available for confirmation a positive Wassermann test, or one of the standard precipitin tests,\* the picture is so nearly complete that there is little chance for error. Surface lesions of the skin or mucous membranes and often the nasal discharges in snuffles will show the *T. pallidum* when examined by darkfield technic. Whenever there is a question as to the validity of the other evidence for syphilis, one can obtain from roentgenograms of the long bones further evidence which may in itself be adequately diagnostic. Well marked increase in density in the zone of provisional calcification with adjacent areas of actual destruction in the metaphysis were not found in any lesion other than syphilis, in our experience, except in one instance where an infant had a subacute sepsis.

Difficulties in interpreting diagnostic laboratory tests are much more likely to be encountered in the cases where one is following the course of

\* What is said subsequently with regard to the Wassermann test will apply as well to other standard serologic tests for syphilis.

infants born to known syphilitic mothers, and where diagnosis is attempted before the actual development of any definitive lesions

It is well established that the infant will as a result of the passage of antibodies across the placenta have a positive blood Wassermann reaction if the mother has a positive blood Wassermann reaction

A "cord" Wassermann test, therefore, would not have any significance with respect to a possible infection in the infant unless it was known that the mother's Wassermann reaction was negative. This possible condition is, however, not found in actual practice

The positive reaction to the blood Wassermann test as a result of a passive immunization from the mother persists for a variable period of time, depending, in all probability, on the degree of positiveness shown by the mother. Observations have been made showing that the positive reaction may last as long as eight weeks. To allow for a factor of safety, it should be assumed that an unsupported positive Wassermann reaction is not adequate evidence of syphilis until the infant is more than three months of age

It should also be emphasized that no unrepeatable serologic test is ever sufficient evidence upon which to diagnose syphilis or to exclude the possibility of syphilis

The infant may, if he is infected, develop a positive Wassermann reaction in a few weeks, or it may be as long as twelve weeks before the Wassermann test becomes positive. This fact allows the formulation of another rule, again allowing extra time for a safety factor. A child with syphilis will invariably have a persistently positive Wassermann reaction by the age of four months if he has not received antisyphilitic treatment. The variations possible in the Wassermann reaction in untreated infants are shown in Figure 83

Treatment given to the mother during pregnancy, and more particularly only during the last trimester of pregnancy, may also be treatment of an established fetal infection. In some instances the infant may develop florid syphilis at the usual time in spite of such treatment. On the other hand, it is quite conceivable that the child's infection might be modified to the point of appearing only after a longer period of time, or of not appearing at all. The development of a positive Wassermann reaction may be delayed many months. One should, therefore, in an infant born to a mother whose syphilis was inadequately treated during pregnancy, continue observation of the infant for a longer period of time, and Wassermann tests should be repeated at six, nine, and twelve months. If the child's Wassermann reaction is negative at twelve months, one may conclude that he either escaped infection or that the treatment during fetal life was adequate



This view may need modification if future experience shows that it is inadequate in any appreciable number of cases

In an infant under three months of age, one may safely await the development of a positive Wassermann reaction, or the time at which the positive reaction becomes significant, if the infant is in apparent good health. If the infant is not thriving, is less than three months of age, and

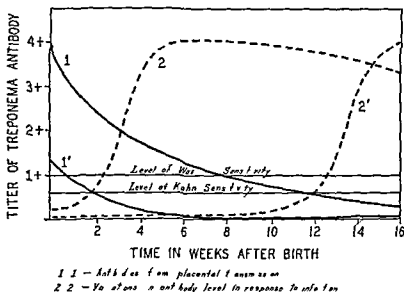


FIG. 83. Diagram showing serologic reactions in congenital syphilis.

if it cannot be shown that the Wassermann test changed from negative to positive, one may rely upon a quantitative increase in the degree of positiveness. Thus, if titration of succeeding tests shows a rising titer of antibody, one may assume that this must be the result of actual infection. One should, however, be exceedingly cautious about accepting minimal increases as being significant.

The fact that active syphilis in the first three months of life is almost invariably associated with osteochondritis makes it possible for one to use roentgenograms to an advantage in doubtful cases. It must be remembered that ill health from any cause may cause increased density in the zone of provisional calcification, and poor calcification of the newly formed bone in the metaphysis. Furthermore, bismuth given to the mother will produce increased density at the end of the long bones of the infant.

## DIAGNOSIS OF LATE CONGENITAL SYPHILIS

The serologic diagnosis of late congenital syphilis is not complicated by the difficulties found in early congenital syphilis. Nor do we find the difficulties associated with the serologic diagnosis of latent and tertiary acquired syphilis. After puberty there may be some tendency for the Wassermann reaction to change to a weakly positive state, and one may rarely see interstitial keratitis associated with a weakly positive Wassermann reaction, otherwise any late lesion which can be established as being syphilitic will be associated with a definitely positive Wassermann reaction.

The diagnosis of congenital syphilis early or late is susceptible to definite laboratory confirmation, and no child should be started on a programme of treatment without indubitable evidence of infection. If treatment was begun, even though it may have been started on inadequate grounds, one has no recourse but to go on to fulfil the minimum of adequate treatment.

## TREATMENT

The treatment of congenital syphilis follows in all essential respects the general principles established for the treatment of acquired syphilis. *Continuous* treatment with alternating courses of one of the arsenical drugs and bismuth or mercury. The small size of the infant and his inability to co-operate may introduce technical difficulties which may alter the choice of drugs and necessitate modification of methods used for treatment. Intravenous therapy is usually impracticable in children under three years of age, and it may be difficult to give bismuth salts by intramuscular injections in small infants. Children enjoy a relative freedom from serious reactions to arsenical therapy. This makes it possible to use in the treatment of children arsenicals that are too toxic to be used in the treatment of adults. Acetarson and sulfarsphenamine belong in this group of drugs. For a description of the various drugs which can be used, see Chapter v.

The following drugs will cover most of the needs in the treatment of congenital syphilis.

**Acetarson** as an arsenical preparation has several advantages in treating infants. It is lower in therapeutic effectiveness than other commonly used arsenical drugs, a fact which makes it very useful in treating early florid syphilis. Its administration is not painful, and this may make it easier to secure the co-operation of parents. After its administration is established, the interval between visits may be made longer than a week and in those who live at a distance from the clinic this may mean the difference between satisfactory and completely inadequate treatment. The fact that the drug is administered at home by the mother is its only serious disadvantage. If one selects patients on the basis of the mother's reliability,

the possible failure of the mother to give the drug will be less trouble than the difficulty of getting patients to return for weekly injections

Acetarsonone is dispensed as a powder which can be weighed out for individual patients or it comes in the form of 0.1- and 0.25 Gm tablets scored for division, which allows a fairly reasonable approximation of doses. The dose is calculated on the basis of 0.1 to 0.05 Gm per pound of body weight, not to exceed 0.4 Gm\*. The daily dose should be dissolved in a portion of the child's formula or other liquid food, and is given by mouth. The use of acetarsonone should be confined to the treatment of infants and it should not be used in treating children older than four years.

Sulfarsphenamine is a very valuable drug for treating congenital syphilis. It should be used where intravenous medication is impracticable, and where one does not want to rely on acetarsonone. Sulfarsphenamine may

TABLE XLVI

SCHEDULE FOR THE TREATMENT OF FLORID CONGENITAL SYPHILIS,  
PARTICULARLY IN EARLY INFANCY

<i>Time</i>	<i>Drug</i>
1st week	0.002 Gm acetarsonone per lb of body weight daily <sup>1</sup>
2nd week	0.005 Gm acetarsonone per lb of body weight daily <sup>1</sup>
3rd week	0.007 Gm acetarsonone per lb of body weight daily <sup>1</sup>
4th through 10th week	0.01 Gm acetarsonone per lb of body weight daily <sup>1</sup>
11th through 14th week	<sup>2</sup> 1 Gm mild mercurial ointment daily <sup>2</sup>
15th week	0.005 Gm acetarsonone per lb of body weight daily <sup>1</sup>
16th through 24th week	0.01 Gm acetarsonone per lb of body weight daily <sup>1</sup>
25th through 28th week	<sup>2</sup> 1 Gm mild mercurial ointment daily <sup>2</sup>
29th week	0.005 Gm acetarsonone per lb of body weight daily <sup>1</sup>
30th through 38th week	0.01 Gm acetarsonone per lb of body weight daily <sup>1</sup>
39th through 42nd week	<sup>2</sup> 1 Gm mild mercurial ointment daily <sup>2</sup>
43rd week	0.005 Gm acetarsonone per lb of body weight daily <sup>1</sup>
44th through 52nd week	0.01 Gm acetarsonone per lb of body weight daily <sup>1</sup>
53rd through 56th week	<sup>2</sup> 1 Gm mild mercurial ointment daily <sup>2</sup>

<sup>1</sup> Acetarsonone is given by mouth. The drug should be dissolved in a portion of the child's formula or other liquid food. The whole of the day's dose may be given at one time.

<sup>2</sup> The mild mercurial ointment should be rubbed into a new skin site immediately following the daily bath.

<sup>3</sup> Substitute weekly injections of 0.03 Gm bismuth subsalicylate in oil intramuscularly whenever it is possible to carry out this treatment.

\* The dose per kilogram in arsenical therapy is in inverse ratio to the total number of pounds. For example a child weighing 20 lb would receive  $20 \times 0.007 = 0.14$  Gm of neocarphenamine while a child weighing 100 lb would receive  $100 \times 0.003 = 0.3$  Gm of neocarphenamine.

be given to children by intramuscular or intravenous injections. The dose is 0.1 to 0.05 Gm per pound of body weight, not to exceed 0.4 Gm.

**Neoarsphenamine or arsenoxide** should be used whenever intravenous injections are practicable. The dose of neoarsphenamine in children is 0.07 to 0.03 Gm per pound of body weight, not to exceed 4 Gm. The dose of arsenoxide is 0.007 to 0.003 Gm per pound of body weight, not to exceed 0.04 Gm (see footnote page 379).

**Bismuth subsalicylate in oil** should be used for heavy-metal therapy wherever the muscle mass is large enough to make injections practicable. The dose is 0.001 Gm per pound in small infants. In older infants the dose is usually 0.03 Gm, in young children two to six years 0.06 Gm, and over six years 0.12 Gm. With such large doses no more than four injections should be given in a course.

**Mild mercurial ointment U.S.P.** fulfils a need in the treatment of young infants who cannot be brought to clinic weekly or who are too small to receive bismuth injections. A piece of ointment the size of a large pea should be applied byunction to the clean skin, at a new site daily, in a dose of 1.0 Gm.

The infant who has florid syphilis presents a problem requiring nice judgement as to therapy. If the child is cachectic, delay in the institution of vigorous therapy may allow his infection to progress to a fatal termination, while too vigorous a schedule of therapy may result in toxic reactions, *resulting from the killing off of large numbers of organisms, and this may be fatal.*

Acetarsonic, because of its low therapeutic index, is almost an ideal drug for the treatment of such infants. Treatment with the drug may be initiated as in the scheme explained in Table XLVI.

When it seems advisable to give all of the treatment in the clinic or the physician's office, the scheme of treatment set forth in Table XLVII may be used.

The above general outline of treatment is usually followed in our clinic. In starting older children, neoarsphenamine or arsenoxide given by intravenous injections is substituted for the sulfarsphenamine. If the patient has manifest lesions it may be advisable to give a four weeks' course of bismuth injections before starting with arsenical medication.

The outlined courses of therapy will usually be adequate for the treatment of early congenital syphilis, but therapy should be continued until two courses have been completed after the persistent reversal of the Wassermann reaction. If the Wassermann reaction is not reversed, treatment may be discontinued after a minimum of two years for those who had normal spinal fluids at the beginning of the treatment. In those who had

TABLE XLVII

SCHEDULE FOR THE ROUTINE TREATMENT OF CONGENITAL SYPHILIS

<i>Time</i>	<i>Drug</i>
1st and 3rd day	003 Gm sulfarsphenamine per lb of body weight <sup>1</sup>
7th day	005 Gm sulfarsphenamine per lb of body weight <sup>1</sup>
2nd through 10th week	01 Gm sulfarsphenamine per lb of body weight weekly <sup>1</sup>
11th through 14th week	1 Gm mald mercurial ointment daily <sup>2</sup>
15th through 24th week	01 Gm sulfarsphenamine per lb of body weight weekly <sup>1</sup>
25th through 28th week	03 Gm bismuth subsalicylate in oil weekly <sup>1</sup>
29th through 38th week	01 Gm sulfarsphenamine per lb of body weight weekly <sup>1</sup>
39th through 42nd week	03 Gm bismuth subsalicylate in oil weekly <sup>1</sup>
43rd through 52nd week	01 Gm sulfarsphenamine per lb of body weight weekly <sup>1</sup>
53rd through 56th week	03 Gm bismuth subsalicylate in oil weekly <sup>1</sup>

<sup>1</sup> Sulfarsphenamine and bismuth subsalicylate in oil are administered by intramuscular injection

<sup>2</sup> The mercurial ointment should be massaged into the skin at a new site each day

spinal fluid changes, treatment should be continued until after a reversal of the spinal fluid Wassermann reaction is obtained, or for a minimum of five years

The treatment of early meningovascular syphilis does not require any special consideration. This lesion will respond to treatment as outlined for early congenital syphilis.

The treatment of late neurosyphilis requires special consideration. These patients should be given fever therapy in addition to other regular treatment procedures. Fever can be produced by giving typhoid vaccine intravenously, by heat cabinets, diathermy, or radiant heat, and by malaria inoculation. The preferable method will depend upon available apparatus, previous training of personnel, and one's own personal experiences.

Tryparsamide is used in the treatment of neurosyphilis. The drug is dangerous in that it may cause optic atrophy. Its use should be limited to those cases where blindness is already present, or to patients who can be carefully followed with regard to their vision, particularly the visual fields.

Intravenous injections of typhoid vaccine are of particular value in treating interstitial keratitis. Starting with 10-15 million bacilli, injections can be given daily. The dose should be doubled with each subsequent injection, or the patient will become unresponsive. A second injection of two thirds the calculated dose after an interval of 20-30 minutes will some-

times give good chills after single injections have failed. Somewhat smaller doses may be satisfactory in the older patients.

Potassium iodide should be added to the other therapeutic agents used in treating tertiary lesions. The drug is given as the saturated aqueous solution, fifteen drops well diluted two or three times daily.

## REACTIONS

Children tolerate treatment with antisyphilitic drugs extremely well. Vomiting during or at the end of the injection is quite common, and need not be regarded as evidence of intolerance. If, however, the vomiting is delayed more than a few minutes, it should be cause for alarm. The dose of the drug should be diminished, and if late vomiting persists the treatment should be changed to another form of the drug. Checking patients by general inspection and by observing weights and temperatures will enable one to find early toxic manifestations and to avoid the production of severe hepatic damage or exfoliative dermatitis. Occasionally blood disturbances occur, such as the development of aplastic anaemia, agranulocytosis, or thrombocytopenic purpura. These phenomena should invariably be regarded as an indication to stop arsenical therapy permanently.

Acetarsone rarely produces the general manifestations of intoxication seen with other arsenicals. It is apt to give rise to diarrhoeal disturbances and the development of diarrhoea should signal the immediate withdrawal of the drug. Usually, one can later put the patient back on the drug by gradually increasing the dose, as in the first course of treatment.

## PROGNOSIS

We pointed out early that diminution of death from congenital syphilis will have to come about principally as a result of the treatment of maternal syphilis.

The child who is found to have syphilis in early infancy who survives this period, and who can be followed to the completion of adequate treatment will in almost all cases be freed of syphilis, though he may develop characteristic stigmata. If his infection is discovered later, increasing difficulty in obtaining reversal of the Wassermann reaction will be encountered.

Persistent reversal of the Wassermann reaction while providing the best available evidence of a cure in syphilis is not always certain, and relapses occasionally occur, particularly within a period of one to two years. Failure to reverse the Wassermann reaction, on the other hand, may not indicate therapeutic failure, subsequent reversals do occur, not infrequently, and

## XV

# MARRIAGE AND SYPHILIS

## HISTORICAL NOTE

APPARENTLY the first extensive discussion of this subject was presented in a series of lectures delivered in Paris by Fournier, the great French syphilologist. Though much of this is outmoded in light of our present knowledge, Fournier drew some pertinent conclusions from his long observation. He pointed out that the syphilitic patient took into marriage the possibility of fatal or disabling tertiary lesions, which might leave a widow with children. He knew these manifestations occurred ten to twenty or more years after infection. Fournier set up the following conditions before a syphilitic subject had a moral right to marry: "(1) absence of existing specific accidents, (2) advanced age of the diathesis, (3) a certain period of absolute immunity consecutive to the last specific manifestations, (4) nonthreatening character of the disease, and (5) sufficient specific treatment." He also said, "If not always, at least in an enormous majority of cases, the husbands that communicate syphilis to their wives are those who have entered into marriage with a *syphilis still young*—that is to say, with a syphilis dating back several months, one year, two years, more rarely three and four years." This was written over sixty years ago.

The question of the relationship of syphilis to marriage arises frequently in the practice of medicine. The subject must be discussed from two viewpoints. First, there is the problem of the syphilitic patient who wishes to marry. The second problem is that of syphilis in a marital partner. This chapter very briefly will bring together certain facts which have appeared elsewhere in this book, and apply them practically in an attempt to answer such questions.

The several facts which must be kept in mind are as follows:

- 1 Syphilis is an infectious disease in which the organism must be transmitted directly from a moist lesion to a moist part in the contact. Practically all infections are thus transmitted by sexual intercourse or by kissing (Chapter II).

- 2 The disease has a tendency to mucocutaneous relapse in its early years (Chapter VIII). The period of probable infectiousness is that of the first four years of the infection, and especially the first half of this period.

- 3 Treatment consisting of thirty or more injections each of arsenic and bismuth, in early syphilis, practically eliminates infectious relapse.

- 4 Adequate treatment is no guarantee against relapse, however. Most instances of infectious relapse after treatment occur within two years of the cessation of treatment.

5 Insufficient treatment—such as inadequate dosage, too few injections, and irregularity in treatment—predisposes to infectious relapse, even more so than does untreated syphilis

6 Everyone exposed to acute syphilis does not become infected

7 The syphilitic woman, even though she is no longer infectious to her spouse, may infect her offspring *in utero* many years after acquiring the disease

8 The syphilitic patient marries with the hazard of possible late disabling or fatal disease which may leave an economic burden on his survivors

Before applying these facts to advice to those either contemplating marriage or who are already married, a brief review of some studies on conjugal syphilis may be of interest

In the historical note, I have already indicated that as long ago as sixty years, Fournier appreciated the importance of the lapse of time in rendering a patient noninfectious. Sir Jonathan Hutchinson pointed out that by the time the sixth year of the infection had been reached, infectiousness no longer occurred. Others have pointed out that women with syphilis acquired before marriage have given birth to syphilitic offspring without having infected their husbands.

With respect to conjugal syphilis, several authors believe that 90 per cent of infected husbands acquire the disease before marriage. Others have estimated that from 65-75 per cent of married women acquire the infection from their husbands. However, in such studies the possibility of extramarital exposures is not given sufficient consideration. In the Vanderbilt University Hospital Syphilis Clinic, Klingbeil and Clark analysed the status of syphilis in 226 couples. Among white patients they found that the husband infected the wife in 50.8 per cent of instances, the wife infected the husband in 13.1 per cent, and that the source could not be ascertained in 36.6 per cent. Among patients of the coloured race the percentages were 33.3, 4.4, and 62.3, respectively.

The relationship of the duration of infection in one spouse to the possibility of transmission to the other may be shown in the following figures. O'Leary and Williams analysed a group of 389 families, and found, if the duration of infection of one spouse before marriage was

of less than 1 year's duration, both partners were infected in 83 per cent  
of less than 2 years' duration, both partners were infected in 33 per cent  
of less than 5 years' duration, both partners were infected in 25 per cent  
of less than 10 years' duration, both partners were infected in 15 per cent  
of less than 15 years' duration, both partners were infected in 9 per cent

They point out that when definite information relative to the time of infection is available, few instances of infection may be accepted as



occurring after a five-year period of time. The incidence of syphilis being what it is, a certain number of marriages will occur in which both partners have syphilis at the time of marriage. Furthermore, extramarital exposures occur.\* These two factors probably account for the small percentage of instances in which syphilis is found in one spouse even though the other had infection of five or more years' duration at the time of marriage. The Vanderbilt University Hospital findings of conjugal syphilis as related to time of infection may be found in Table XLVIII.

O'Leary and Williams cite seventy families in which one spouse had acute syphilis at the time of observation. In 64 per cent of these, the partner had acute syphilis, 22.7 per cent had early latent syphilis, and 10 per cent had early neurosyphilis. Only two partners of spouses with acute syphilis were found to have late syphilis. Table XLIX shows the stage of syphilis in the 226 original patients and their marital partners as found by Klingbeil and Clark in our clinic.

Acute syphilis may appear in one, and yet the other spouse may escape infection. In the study of O'Leary and Williams, 170 husbands and 18 wives acquired infection by extramarital exposure. Eventually, 76 per cent of the wives of the 170 men became infected, whereas 50 per cent of the husbands of the 18 wives acquired the infection. These authors admit that factors which were not analysed may account for escape from infection in some. Such factors may be marital incompatibility, contraceptives, impotency, etc. However, they point out that three couples had repeated intercourse, without the use of prophylaxis, at the time mucosal lesions were present without transmission of the disease. In the material from our clinic Klingbeil and Clark found that five marital partners escaped infection by a chancre in the spouse, and thirteen did not become infected from a partner in the secondary stage of syphilis. Thus 18 of 96 marital partners escaped infection, even though the spouse had mucocutaneous lesions. In all instances they were living together, though it is not known whether unprotected sexual intercourse occurred or not.

The matter of treatment and relapse is important. No satisfactory data of any consequence are available. O'Leary and Williams found that among eighteen patients, who had received twenty or more injections of arsphenamine and bismuth in the first year of infection and who had married before the disease was two years old, six of the partners became infected (33 per cent). The frequency of infection in marital partners of inadequately treated spouses was 40 per cent. In our clinic, as shown in Table XLVIII, infection of the partner was more frequent if the spouse had been treated (inadequately in each instance) than if untreated.

\* In the Vanderbilt group, marital infidelity was admitted by 53 per cent of white men, 7 per cent of white women, 45 per cent of Negro men and 28 per cent of Negro women.

TABLE XLVIII  
THE EFFECT OF DURATION OF INFECTION AND OF PREMARITAL TREATMENT ON THE  
INCIDENCE OF CONJUGAL SYPHILIS<sup>1</sup>

Spouses of Original Patients	Original Patients—Duration of Disease Before Marriage					
	Less than 4 Years			4 Years or More		
	Untreated		Treated	Untreated		Treated
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Spouse infected	1	12.5	5	41.6	0	0.0
Spouse escaped	7	87.5	7	58.4	13	100.0
Totals	8	100.0	12	100.0	13	100.0

<sup>1</sup> From Ven Dis Inform

TABLE XLIX

THE TYPE OF SYPHILIS IN 226 ORIGINAL PATIENTS AND THEIR MARITAL PARTNERS<sup>1</sup>

State of Disease of Wives	Stage of Disease of Husbands										Totals
	Negative	Primary	Secondary	Early Latent	Late Latent	Latent—Dura- tion Unknown	Benign Tertiary	Asymptomatic Neurosyphilis	Symptomatic Neurosyphilis	Cardiovascular	
Negative	0	4	8	4	18	1	2	4	11	2	54
Primary	1	2	0	1	0	1	0	0	0	0	5
Secondary	5	3	22	8	1	4	1	0	0	0	44
Early latent	5	1	6	11	3	4	0	0	0	0	30
Late latent	20	0	1	1	10	14	0	1	1	0	48
Latent—duration unknown	3	0	0	2	12	3	6	2	3	0	31
Benign tertiary	1	0	0	0	0	2	0	0	0	0	3
Asymptomatic neurosyphilis	3	0	0	0	0	1	0	0	0	0	4
Symptomatic neurosyphilis	4	0	0	0	0	2	0	0	0	0	6
Cardiovascular	1	0	0	0	0	0	0	0	0	0	1
Totals	43	10	37	27	44	32	9	7	15	2	226

<sup>1</sup> From Ven Dis Inform

## SYPHILIS AND CONTEMPLATED MARRIAGE

The physician frequently must advise the syphilitic patient regarding contemplated marriage. He can be logical in his advice if he will give consideration to what has gone before in this chapter.

## SYPHILIS IN BOTH PARTNERS

The matter of the marriage of two syphilitic persons comes up not infrequently among the clientele of the public health or hospital clinic. Often the disease has been acquired by one from the other during the intimacies of courtship. There is no reason why such couples should not marry. However, they should be urged to take thorough treatment, not only for their own health but especially for the woman, to protect future offspring from the disease. I believe it is best to advise contraception for two or three years, thereby giving the disease an opportunity to become quiescent. It must be clearly understood that the woman must again present herself for treatment if she becomes pregnant any time after having completed treatment.

## SYPHILIS IN THE MAN

Knowledge of the natural course of syphilis and available clinical information makes it safe to state that the untreated syphilitic male who has had syphilis for four or more years may marry without endangering his bride.

In syphilis of less than four years' duration, with antisyphilitic treatment begun during the acute stage, advice will vary depending upon the following circumstances:

1. Given a patient who has received thirty or more injections each of arsenic and bismuth with regularity and in adequate dosage, whose blood became negative within the first six months of treatment so that he had a year of therapy subsequently, and whose spinal fluid and blood have remained negative one to two years after the cessation of treatment, *permission may be given for marriage*. Such an individual will have had syphilis for 2.5 to 3.5 years or more, will have had "adequate" treatment, and will have been seronegative for two to three years. Only rarely will relapse occur in such a person, with danger to the spouse. The physician must protect himself by stating that this possibility exists.

2. Given a patient with syphilis of less than four years, who began antisyphilitic treatment during the acute stage, took it only for some months, or with great irregularity. Here the danger of relapse is so great that the physician has no choice but to advise a full course of treatment,

and to permit marriage only after a two-year period of careful observation subsequent to the cessation of treatment.

3. If latency has been definitely established even though early—as, for example, in untreated syphilis of twelve or eighteen months' duration—the danger of relapse is small. It therefore seems that the man with such early latency may be permitted to marry after having completed a full course of so-called adequate therapy (thirty injections each of arsenic and bismuth), with a year of careful observation subsequent to completion of treatment.

#### SYPHILIS IN THE WOMAN

What has been said with respect to syphilis in the man is applicable to syphilis in the woman. However, the additional aspect of pregnancy as related to syphilis must be considered. Contraception should be advised for the first year or two of marriage. Thereafter, the disease being more quiescent, a child conceived later in the course of syphilis is less likely to be infected. Furthermore, the woman must be instructed to inform her prospective husband of her disease, since she must be treated during pregnancies. It is wiser to have this understood before marriage than to disclose the matter later. At times the woman lacks the courage to inform the husband, and takes no treatment. Presenting him with a syphilitic child in such an event is a tragedy.

In early syphilis, in either sex, if during the period of observation subsequent to the cessation of "adequate" treatment, mucocutaneous or neuro-relapse occurs, the only choice is to apply the suggestions made for the original acute infection. Serorelapse in treated early syphilis must be evaluated in the individual case, with respect to advice for marriage.

Though we may give advice, it does not necessarily follow that it will be accepted, and it is difficult to know what to do at times. For example, no good answer presents itself to the question posed at times by one or other of the couple, when marriage is advised against, "Why can't we get married when we're having intercourse anyway?" For practical purposes they might as well marry, and yet if the uninfected partner develops the disease, the physician may be blamed for giving permission. A girl's parents especially might blame the physician, not being aware of the fact that their daughter and her fiancé were having sexual intercourse.

And then again, we have known of men who, when forbidden to marry, have broken their engagement, and have become irregular in treatment. They have become indiscriminate in their love affairs, exposing numbers of girls and women to their disease through kissing as well as sexual intercourse.

It is also worthy of emphasis that, even though all danger of infectious-

ness is past, the syphilitic patient, contemplating marriage, should in all justice inform his prospective mate of his disease. He should do this because of the possibility of disability or death due to late manifestations, which might leave an economic burden upon the marital partner. The status of the syphilitic individual in this respect is the same as that of the patient with tuberculosis, rheumatic heart disease, or diabetes mellitus.

The question often arises, whether a physician can stop a marriage in which the patient does not abide by his advice? Furthermore, is the physician legally liable if he does not do so? Apparently there is no uniformity as among the several states, with respect to these legal questions. In some states physicians are specifically released from professional secrecy if necessary to prevent marriage of those having venereal disease in a communicable state. Again, a physician may be legally liable if he permits marriage of a syphilitic patient who may transmit the disease to the spouse. Several states have set up statutes outlining the circumstances under which syphilitic persons may marry. They are less stringent than those given in the preceding paragraphs, which are more or less ideal, and cover most exigencies.

### SYPHILIS AFTER MARRIAGE

When syphilis is acquired by one of a married couple, the problem is different than in the case of contemplated marriage. Usually infection is due to infidelity, and this in itself may lead to separation or divorce. Marriage may occur at a time when one partner is incubating the disease, and thus the infection may be missed by premarital blood tests. Under such circumstances the patient is marrying in good faith. Occasionally, innocent infection occurs in married persons, of which several instances have been described in previous chapters. If the presence of syphilis has not led to separation, which may be excused only in infidelity, the physician's problem is to so advise as to prevent infection in the marital partner.

The infected partner must inform his spouse of his disease. He may wish to enlist his physician, a social worker, or public-health nurse to assist in this. No attempt should be made to keep the presence of the disease secret, for almost always something occurs sooner or later to arouse suspicion in the spouse and then recriminations begin because of the dishonesty or lack of frankness which was shown.

Obviously, advice of sexualabstinence over the period of possible relapse, as given in the section on contemplated marriage, would be ridiculous. Few marriages would survive this. Philosophically speaking, marriage at best is a hazard and a gamble, and I believe few married persons would refuse to take chances which might prevent a family circle from breaking.

up Therefore the physician must recognize that if the family is to remain intact he cannot interdict sexual intercourse for two- or three-year periods. In general, the intelligent patient is usually co-operative in following out antisyphilitic treatment in his desire to spare his partner from infection.

Given a patient discovered to have acute syphilis, the management should be somewhat as follows. The marital partner often has been exposed before infection was discovered. Therefore, repeated examination of the spouse both physically and with blood tests is essential, until such time has passed that this is not necessary. (If secondary syphilis is the first recognized stage, the children also should be examined and observed in the same way.)

Treatment of the acute syphilis in the infected partner must be regular and adequate as to number of injections of arsenic.

Sexual intercourse and kissing must be prohibited, at least during the first course of arsenic and bismuth. (The latter, as was shown in earlier chapters, is a period when relapse may occur.) If the lesions healed promptly, the blood has become negative, and treatment is regular, sexual intercourse may be permitted after the first few injections of the second arsenic course. However, intercourse should be permitted only with a condom which must be worn during the whole period of sexual contact. Thus a period of about four months is a minimum period of abstinence. If continence can be practised until the third course of arsenic is begun, a period of seven months, so much the better. Sexual intercourse without a condom should be prohibited, not only during the time of treatment, but also during the year subsequent to the cessation of treatment. If the blood and spinal have been negative during this time, as well as during a year or so of the treatment period, sexual contact may be permitted without protection.

Observation and blood tests must be frequent for two or three years following treatment to note signs of relapse as early as possible. The uninfected partner should also be carefully checked at intervals.

So far, the discussion of syphilis in one marital partner has been limited to the management in the presence of early syphilis. If untreated syphilis of more than several years (three or more years) is found in one marital partner, only one examination of the spouse is necessary, and if this is negative, no further follow-up study need be done. The couple should be permitted to carry on their sexual relationships as before. Since the infected partner is beyond the time of probable infectiousness, he is of no danger to his spouse. (See Table XLVIII.)

The marital partner who has had inadequately treated syphilis of less than about four years' duration is potentially dangerous to his spouse in the event of relapse. Even though his marital partner is found to be

negative, subsequent examinations may be indicated. Treatment of the infected partner should be instituted.

In conclusion, it should be emphasized that the physician must know the biologic course of the syphilitic infection so that he may be rational in his advice to his patients with regard to syphilis in marriage. He must be rigid in his advice to the infected person contemplating marriage unless the couple has been indulging in antemarital sexual relationships. In early syphilis in one of marital partners, "the cards should be laid on the table." Both partners should know what precautions are essential, and both should realize possible dangers, realizing that their happiness may be worth the taking of some chances. Late syphilis in one marital partner offers no contraindication to normal sexual relationships.

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## XVI

# ADMINISTRATIVE MEASURES IN THE PREVENTION AND CONTROL OF SYPHILIS

BY ALVIN E. KELLER, M.D.

## HISTORICAL NOTE

WHILE no concentrated effort was made to control syphilis prior to ten or twelve years ago, that aspect of syphilis was emphasized as early as 1876. Marion Sims, as President of the American Medical Association that year, in his presidential address stated that "in cholera and yellow fever, and in smallpox and syphilis, we recognize cruel and fatal diseases, easily communicable, each attacking the human family in its own peculiar deadly way, and we propose to deal with them all in the same manner, taking the surest, safest, and quickest method of protecting the community against their pestiferous presence, and of preventing their spread among the well." This is the same viewpoint with reference to the control of syphilis as is held to-day. His paper was published in the *Journal of the American Medical Association*, but no official or unofficial action followed that statement.

Herman Biggs, health officer of both the state and city of New York, was aware of the public health problem of syphilis. However, the World War of 1914-1918 prevented him from attempting the institution of control measures against syphilis. The administrators of the military services, however, were aware of the prevalence of venereal disease in our forces during the war. In 1918 the Congress created and provided for a Division of Venereal Disease within the United States Public Health Service through the passage of the Kahn Chamberlain Act. The objective of that law was to assist the states with the control of venereal disease. From that time until 1935, the appropriations for that activity were relatively small and insufficient to provide for any intensive programme of control.

In 1935, under the strong and effective leadership of Parran, who, first as State Health Commissioner of New York and then as Surgeon General of the United States Public Health Service, presented clearly to the people of the United States the facts relative to syphilis as a problem of public health. Through his efforts funds were made available by the Federal Government to the states for a programme of control through Title VI of the Social Security Act. To provide stability for the venereal-disease programme by the Federal Government, Congress passed the LaFollette-Bulwinkle Bill in 1938, known as the Venereal Disease Control Act. Congress is thereby enabled to appropriate annually funds to be allocated to the states under certain stipulations for the control of venereal diseases. This made it possible to plan a nationwide programme over a long period of time.

Syphilis is a communicable disease, and should be treated as such by physicians and public-health administrators. In a country with conditions and population groups so diverse and varied as are found in the United States, it is difficult to apply a single plan of control of syphilis. In each state, county, and city the problem must be studied and a plan of action developed to meet local needs. However, there are certain principles upon which the control of syphilis may be based and which may have general application. These measures may be stated as follows: (1) administrative measures, (2) medical measures, (3) case finding and case holding, and (4) educational measures.

The setting up of administrative measures and the provisions for carrying them out are the responsibility of the Federal, state and local governmental units. The efficiency of a syphilis-control programme in a state or local health department will depend in large measure upon the interest and support of the Federal government in such a programme. It has already been pointed out that the United States Public Health Service receives funds through the Federal Security Agency for such purposes. This was made possible through the passage of the Venereal Disease Act in 1938. The funds which the states receive from the Division of Venereal Disease of the United States Public Health Service are allocated on a matching basis, but when the syphilis problem is of great importance or where the population to be served is large, the state or local area may receive additional funds. This financial support from the Federal government may be used by a state health department for (1) the provision of additional personnel, (2) the training of medical, nursing, and technical personnel, (3) the purchase of drugs for the treatment of venereal diseases, and (4) the extension and improvement of the serologic divisions within state public-health laboratories.

In addition to financial support to state health departments, the Venereal Disease Division of the United States Public Health Service has conducted research programmes, and provided for investigations within the states and in various institutions. The results of such work has been of value, and in some areas it has been possible to apply the important findings to venereal programmes already in operation.

The United States Public Health Service has assisted state health departments with medical and nursing personnel by assigning to the states service officers who work under the direction of the administrator of the state health department.

As a result of the careful work of the Committee on Evaluation of Serodiagnostics tests in the United States, a large proportion of public-health laboratories furnish serologic and diagnostic service which meets the standards of sensitivity and specificity as set up by that Committee.

Evaluation studies tend toward a uniformity of procedures between a majority of state laboratories so that in time reciprocity between the states in regard to premarital blood testing may be facilitated

In May 1940 the Conference of State and Territorial Health Officers adopted an agreement which was developed by the War and Navy Departments, the Federal Security Agency, and the state health departments for the control of venereal disease in areas where armed forces or national-defence employees are concentrated. This agreement was developed to secure more efficient diagnosis and treatment of acute cases of venereal disease, to establish a more satisfactory system of reporting of contacts, and to reduce exposure to and contact with infected individuals.

In December 1941 it was announced that a Division of Social Protection had been established in the Federal Security Agency for the purpose of safeguarding the health and morals of the armed forces and the workers in the defence industries. The objectives of this new Federal programme of social protection are (1) repression of commercialized prostitution, (2) treatment of prostitutes, (3) protection of women in defence areas, and (4) co-operation with other agencies. This programme, as in the case with other Federal agencies, will be conducted in co-operation with public officials, private agencies, and interested citizens.

The control and prevention of syphilis from the state level rests usually upon the state health departments. Since the efficiency of the venereal-disease-control programme in local areas depends in large measure upon the support received from the state health department, it is necessary to provide and administer an effective state programme for this purpose. The venereal-disease programme of a state should be placed as a subdivision or section in the division of preventable disease. In some states and cities separate divisions or bureaux are developed for this purpose. In any event there should be a well trained, full time physician in charge of this activity. He should be given the responsibility for the conduct of this programme, and should be provided with sufficient personnel—medical, nursing, and clerical—to assist the local public-health agencies and counties without full-time health departments to operate effectively.

According to a report of an advisory committee to the United States Public Health Service, revised April 15, 1941, the state health department programme or the venereal disease division in large municipal health departments should perform the following functions: "(1) a definition of the aims, purposes, and policies of the venereal-disease programme, (2) the collection and analysis of morbidity data, (3) the establishment of effective co-operation with physicians in private practice, (4) the development of cordial relations not only with the public but also with special scientific groups, (5) administrative consultation to other units within the health department, such as the

laboratory section, the maternal and child health section, and the industrial hygiene section, (6) the organization and supervision of venereal disease-clinics, (7) the organization and supervision of epidemiologic and follow-up services for clinics and private physicians, and (8) study of and control of the efficiency of venereal-disease clinics in terms of contact tracing, efficacious treatment, and case holding "

The state health departments have other functions to perform in addition to the ones advocated above. The distribution of drugs to local and municipal health departments for use in their own clinics and for distribution to physicians and other treatment agencies, has become an accepted practice. At present this is provided by the state health departments without cost to the local public-health agencies. Physicians may secure drugs from their local health department.

The state health department is solely responsible for the type of legislation passed for the purpose of controlling venereal diseases within its boundaries. At the present time laws relating to this medical problem are by no means uniform throughout the United States. This leads to confusion in interpretation and laxity in enforcement when resort to legal steps becomes necessary. Many of the statutes are obsolete in the light of present-day knowledge of syphilis. Some of the recent legislation is discriminatory, and places hardships upon patients having syphilis. The public, on the other hand, is given a false sense of security with respect to domestic employees, food handlers, and related groups in regard to the safety provided by a "health card" which states that the blood test is negative. In our experience state employees included in the above categories have at times been discharged upon presenting cards which indicate a positive test. Such practices at times lead patients to employ subterfuges. *In our opinion this type of legislation does not aid materially the control of syphilis. Nor does it afford much protection of the public against communicable diseases if the domestic servant has a negative blood test and far advanced pulmonary tuberculosis. The protection of the public against communicable disease can be obtained best through educational measures.*

During the past few years state legislatures have passed laws requiring premarital and prenatal blood tests. The purpose of such statutes is to prevent (1) syphilis in the respective marital partner, and (2) prenatal syphilis. There is no uniformity of such laws in the states where they are on the statute books. Up to June 1941 twenty five states required the examination by a physician and a blood test of both marital partners, four states required examination by a physician to determine the presence of a venereal disease, three prohibit marriage of persons with venereal disease. Some states require a personal affidavit of freedom from venereal disease, no examination is specified. It has been stated in Chapter xvii that less

than 2 per cent of persons to whom the premarital laws apply have been found to have positive blood tests Brunet and Salberg have stated that 500 of 913 women applying for premarital examination admitted sexual exposures Such legislation therefore cannot prevent infection

There are many objections to premarital blood testing laws as they appear at the present time, among which is the fact that the public believes it is getting protection from venereal diseases by this procedure It places the physician in a position of relying on the patient's word, and upon the accuracy of the laboratory In some places the sole responsibility for the interpretation of such laws rests with the laity, and not the medical profession It has been advocated by Snow that a model premarital blood-testing law be developed and presented to each state for approval This would seem to be a sound procedure Nelson has stated that premarital examinations will be of value when candidates for marriage go to their own physicians because they want a thorough examination and are willing to accept the best opinion that the physician can give

Up to June 1941 twenty-five state legislatures had passed a law requiring physicians to include a blood test as a part of the examination of every pregnant woman coming under their supervision The physician must state on the birth certificate that a blood specimen was secured from the mother, but he is not required to indicate the result of the test This type of legislation can be of great value from a public-health standpoint because the prevention of prenatal syphilis is based on sound scientific data, and will receive the support of the medical profession In New York state exclusive of New York City, 96.5 per cent of 84,475 birth certificates recorded in 1939 indicated that blood tests had been performed on the mother Of these, 76.3 per cent were secured during pregnancy, and 20.2 per cent were obtained at the time of delivery In 41 per cent of the cases the tests were made during the fifth month or earlier This practice should become generally accepted over the country either as a result of education or legislation

The Committee on Evaluation of Serodiagnostics Tests for Syphilis in the United States has pointed out that public health laboratories perform only 25 to 50 per cent of all the blood tests for syphilis in this country The remainder are done in a variety of institutions and private laboratories Obviously, the accuracy of tests performed by these laboratories depends upon the experience of the director of such work, the training of the technical personnel, the type of procedure used, and the efficiency of the administration of each laboratory For some time state health departments have assumed the responsibility of checking the serologic blood tests performed in such laboratories in order to insure uniformity of procedure This will no doubt provide additional safeguards for the public in the

diagnosis of syphilis. A state can do this only after its state public-health laboratories are brought up to the standards set forth by the United States Public Health Service. This movement has already gained impetus, and several states have already certified the serologic tests performed by other laboratories with the state. Lists of laboratories approved by the state health department are furnished periodically to physicians. This procedure should be extended by state health departments, and conducted preferably on a voluntary and co-operative basis, but by legal provisions if necessary.

A state health department has certain obligations to county health departments in the conduct of local public-health programmes. State health departments should assist in the following ways: (1) financial support, (2) furnishing public-health laboratory service and therapeutic agents, (3) technical advice and supervision, and (4) consultation regarding special problems. This assistance is applied to venereal-disease control. Where special problems related to venereal diseases are present in a local area, the state health departments usually take this into account and render additional assistance.

Table L shows the activities of the state health departments in relation to syphilis control for the period 1938-1941, inclusive.

TABLE L

VENEREAL-DISEASE CONTROL ACTIVITIES OF STATE HEALTH  
DEPARTMENTS, 1938-1941

Fiscal Year		Number of Clinics	Number of <i>Syphilis Cases</i>		Serologic Tests <sup>1</sup>	Doses of <i>Arsemicals</i> <sup>1</sup> Distributed
			Admitted to Clinics			
1938	. .	1,122	149,434	3 6	2.8	
1939	. .	2,085	249,464	5 6	4.7	
1940	. .	2,454	288,778	10 2	6.9	
1941	. .	3,245	340,615	16 5	8.2	

<sup>1</sup> In millions

The programme of venereal-disease control in local areas is administered by either municipal health departments, full-time county health departments, combined city-county health departments, or by the state health department where full-time health units have not been established. The local administrative units render service directly to the population, and receive the assistance of the central office according to the provisions for the control of syphilis arranged by the state health department. Upon the

local health department, therefore, rests the responsibility for the effectiveness of the control of venereal diseases

The full time health officer usually directs the entire programme. In municipalities responsibility for syphilis control may be placed upon the director of the division or bureau of venereal diseases. In a county health department the health officer working alone or with the aid of an assistant is charged with the conduct of the entire public health programme, of which syphilis control is only one part.

The programme of venereal-disease control conducted by a local health department should include (1) routine collection of morbidity data, (2) clinical and diagnostic facilities, (3) distribution of drugs to designated persons, (4) case finding and case holding, (5) consultation service for physicians, industrial organizations, and other groups, and (6) an educational programme.

In the matter of morbidity reporting, the physician should recognize his obligation as a practising physician, and promptly report cases of communicable diseases seen in his practice. The same statement applies to institutions and hospitals, since they are held responsible under the state public health laws in the same manner as physicians. No health department can control communicable diseases without this vital assistance. The mechanism set up for this purpose may vary in some details from state to state, but as a rule a minimum of information is requested and the filling out of report forms requires but little time.

The Advisory Committee to the United States Public Health Service recommends a notification reference to syphilis and other venereal diseases which would show the following minimum data:

- 1 Date of report
- 2 Name or initials or identification number of patient
- 3 Address of patient
- 4 Age or date of birth, colour, and sex of patient.
- 5 *Duration of infection*
- 6 Diagnostic classification

For Syphilis

- Acquired Primary—Secondary
- Early Latent (less than four years' duration)
- Late Latent (more than four years' duration)
- Congenital (specify manifestations)

For Gonorrhea

- Genital, Eye and other
- Chancroid
- Granuloma inguinale
- Venereal lymphogranuloma (lymphopathia venereum)

- 7 Laboratory confirmation of diagnosis (darkfield, blood, smear, culture, Frei

test or intracutaneous test for chancroid, reported as positive, doubtful, negative, or not done)

- 8 Information concerning amount of previous treatment
- 9 Statement as to whether or not patient with syphilis is pregnant at time of beginning treatment (if pregnant, months pregnancy has advanced or the expected date of confinement)

The above information is furnished to health departments by physicians and other treatment agencies on a card prepared for this purpose by the United States Public Health Service. It can be mailed to the health department in a self-addressed franked envelope. The notification system should also provide for, or take into account, (1) the reporting of patients delinquent in clinic attendance, and (2) contacts of acute cases.

Treatment facilities as provided by local health departments are fundamental in the control of syphilis. This service is rendered in clinics which are usually located in the health department. In large municipalities the venereal-disease clinic service may be decentralized, and facilities situated in sections of the cities where the venereal-disease prevalence is greatest or located in health centres which are considered as branches of the health department. In some rural health departments the same plan is used in order to make treatment more easily accessible to the patient.

To facilitate the treatment of patients, mobile units have been developed. These units consist of a specially built truck and are equipped to perform a variety of public-health services in addition to the treatment of syphilis. Either personnel especially trained for this type of activity or the regular employees of the health department are assigned to the units of this type.

Another plan of rendering clinic services to rural areas is that of traveling treatment teams. These usually consist of a physician and a nurse who travel regularly over a circuit and administer antisyphilitic treatment at established places in one or more counties. This plan relieves the county health officer of a great deal of routine work, and enables the staff of the health department to spend whatever time is available for case finding and education. In some areas practicing physicians assist in clinics conducted by the health department. For this service they are reimbursed through the health department on a clinic or hourly basis.

Many functions related to venereal-disease control may be performed in clinics aside from merely the treatment of the patient. Too frequently, this particular aspect has been considered, by venereal-disease control officers, as the only purpose to be served by clinics. Among the other important objectives of syphilis clinics is case holding. This is just as important as case finding. Keeping patients under treatment in clinics can be done by educating the patient as to the necessity of taking regular treatment, and by the use of proper technic in administering treatment.



The treatment room is the place where more patients may be lost than in any other subdivision of the clinic. In the clinic the most favourable opportunity is available for education of the patient. He is most receptive to information concerning his disease, especially in the early days of his treatment. If the patient can be properly instructed and assisted in arranging for his treatment early in his clinic experience, a great deal of time may be saved in making visits to delinquent patients. Case finding always originates in the clinic or in the office of the physician. Information relative to contacts may be more readily obtained from the patient by tactful questioning in the early stages of his treatment than subsequently.

Municipal clinics and university hospital clinics have made important contributions in the epidemiologic and clinical aspects of syphilis. In addition to research, clinics of this type have been active in the training of public-health personnel who are to engage in venereal-disease control.

Clinics should receive for treatment (1) patients referred by physicians, (2) patients coming to the clinic with an emergency condition, and (3) patients referred by physicians for special services, as for consultation. It should be the policy of public-health clinics, especially in rural areas, to accept patients for treatment only upon reference in writing by physicians. Clinics should be so arranged as to offer the patient reasonable privacy during examination and treatment. The number of clinics required in an area depends upon the extent of the problem, and a sufficient number of clinic sessions should be held to allow for good medical practice.

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## XVII

# EPIDEMIOLOGIC FACTORS IN THE CONTROL AND PREVENTION OF SYPHILIS

BY ALVIN E. KELLER, M.D.

### HISTORICAL NOTE

SYPHILIS is a communicable disease transmitted from person to person. The application of this knowledge to the control of syphilis, however, was not demonstrated until 1933. This was due to the modes of transmission which are usually associated with intimate relationships between persons and the lack of effective methods of approach to exposed individuals. In communicable diseases (such as tuberculosis, diphtheria, and typhoid fever) public-health investigators have no hesitancy not only in searching out exposed individuals, but also in applying efficient laboratory procedures and in keeping such individuals under investigation for a sufficient period of time to determine whether or not they are carriers of infectious agents or are suffering from the disease in question.

Munson, a former district health officer in New York State, by tactful and persistent investigation of contacts of acute cases of syphilis, was one of the first to apply the same principles of case finding in syphilis that are applied to the other common communicable diseases. He demonstrated clearly that syphilis appears in a community as localized epidemics originating from one or more foci of infection, and that each infected person was potentially a focus of an epidemic. This work was done in small communities. Nelson in Massachusetts, Smith and Brumfield working in a small city and in rural areas of Virginia, and Clark in a moderate-sized town in Tennessee have applied the same procedures as those used by Munson. All these investigators have confirmed Munson's opinion. Webster and Shelley in New York City have recently shown that it is possible successfully to apply epidemiologic procedures in syphilis case finding in a city of that size. By the proper approach to the contacts, both sexual and household, it is possible to find other individuals with acute syphilis and to place them under treatment, and also to keep exposed persons who have not developed the disease under supervision for a sufficient period of time to determine whether they will develop syphilis.

### BASIC EPIDEMIOLOGIC FACTORS

Epidemiology may be defined as a study of conditions known or reasonably supposed to influence the occurrence and prevalence of any disease. The basic epidemiologic factors essential to a study of an infectious disease are (1) the reservoir of infection, (2) the etiology of the disease, (3) the

susceptibility of the population, (4) the modes of transmission and pathogenesis, and (5) the immunological aspects or host-parasite relationship

### THE RESERVOIR OF INFECTION

These points will be discussed with reference to syphilis. In regard to the reservoir of infection man represents the sole focus of infection. The extent of the reservoir of infection in the population cannot be stated accurately.

### THE SUSCEPTIBILITY OF THE POPULATION

The following figures for the prevalence of syphilis in the United States are based upon estimates. Among the white population it varies from 1.3 to 2.4 per cent, and for Negroes is about 11.9 per cent. In the urban population 2.9 per cent are infected. In the rural sections 1.8 per cent have syphilis. Available data reveal that syphilis is more prevalent among white males than among white females, whereas among Negroes it is more frequent in coloured females.

The above data may be expressed in another manner, viz., that one in forty-two persons in the United States has syphilis, the ratio for white persons being one in seventy-seven while that for Negroes is one in every eight. In urban areas one in every thirty-four persons is estimated to have syphilis, while in rural areas the ratio is one in every fifty-six.

It may be of interest to note that in industrial populations, among 425,000 workers in 800 plants in 25 communities, on whom blood tests were made, 3 per cent of the tests were positive. Of persons examined for syphilis, usually by blood tests, under the existing premarital examination regulations, less than 2 per cent have been found to be positive. Data with respect to prenatal blood tests are not so complete for pregnant women as they are for the other groups in the population, but reports from thirteen states (only two of which are Southern states) show that 1.67 per cent had positive tests. The thorough investigation of every pregnant woman for the presence of syphilis is one of major importance in the prevention of congenital syphilis. That this is necessary is shown by the fact that approximately 96,000 children were born to syphilitic mothers in the United States in 1940. Of that number, 34,000 had congenital syphilis. While good results have been obtained in this phase of syphilis control, much remains to be done.

Though Parran and Vonderlehr estimated that there were 3,200,000 persons who had syphilis in the United States in 1941, it should be pointed out that this represents the total number of infected individuals. This represents an accumulation which has occurred over many years, and does not mean that all persons found to have syphilis are in the infectious, or

potentially infectious, stage of the disease. No accurate information is available for the number of new infections acquired annually, or the number of persons who are in the first four years of their infection. The latter groups and pregnant women represent the infectious reservoirs in the population.

A majority of syphilitic infections are acquired early in life. Of syphilitic patients at least 50 per cent acquire the disease before the age of twenty-five years, and 80 per cent before the age of thirty years. Negroes usually become infected at an earlier age than white persons. In the first million selectees and volunteers given blood tests during 1940 and 1941, 45.2 per 1,000 had positive tests. The rate for white selectees or volunteers was 18.5 per 1,000, for Negroes was 247.7 per 1,000. These men were between the ages of twenty-one and thirty-six years. The same data reveal the highest prevalence rates in the Southern states and the District of Columbia (Table LI).

TABLE LI

THE PREVALENCE OF SYPHILIS IN THE SELECTEES AND IN THE  
GENERAL POPULATION ACCORDING TO GEOGRAPHIC AREAS

Region	Selectees Rate Per 100 <sup>1</sup>	General Population	
		Estimated Rate Per 100 <sup>2</sup>	Estimated Number of Cases <sup>2</sup>
United States	4.5	2.4	3,171,861
16 Southern states and D. C.	10.3	4.6	1,904,365
South Atlantic	11.3	5.3	952,651
East South Central	10.3	4.2	454,619
West South Central	9.2	3.8	497,095
32 Northern states	2.1	1.4	1,267,496
New England	1.1	0.6	53,471
Middle Atlantic	2.2	1.4	376,201
East North Central	2.3	1.6	415,971
West North Central	1.7	1.2	168,612
Mountain	2.8	2.0	81,406
Pacific	2.7	1.8	171,835

<sup>1</sup> Males aged 20-35

<sup>2</sup> Males and females, all ages

The biologic characteristics of the *T. pallidum* have been discussed in Chapter II. The organism can penetrate and invade tissue, surviving and retaining its virulence only in living tissues. It has the ability to live in symbiosis with the host, and can withstand very strong attacks by chemotherapeutic, nonspecific antibodies and physical agents. *T. pallidum*

requires moisture and living tissue for its multiplication and survival. The organism dies quickly when dried, it is destroyed by soap and water.

#### THE MODES OF TRANSMISSION AND PATHOGENESIS

Syphilis may be transmitted by direct contact, indirect contact, prenatal infection of the fetus, and inoculation of blood containing spirochetes (as in transfusion, or in surgical accidents )

**Direct Contact** By far the greatest number of infections are acquired by direct contact with lesions containing treponemata. The most favourable types of lesions are those which are moist and accessible to exposed persons. Because lesions in or on the genitalia and in the mouth have an abundance of moisture, erosions occur which open the lesion and allow the *T pallida* to escape. Though the organism can be demonstrated in skin papules if scarified sufficiently to obtain serum, transmission of syphilis by such lesions would be practically impossible. Contact with lesions containing large numbers of treponemata (mucous patches and moist genital lesions) leads to infection in a high percentage of exposed individuals. No data are available as to the percentage of persons who escape infection when exposed to moist lesions. In some instances infection may not occur because the number of organisms was too small. In the Vanderbilt University Hospital Syphilis Clinic about 25 per cent of contacts of acute cases of syphilis escaped infection. However, the conditions, such as the time of exposure in relation to the appearance of the infectious lesion and the use of prophylactic agents during such exposures, should be studied more carefully.

Since the transmission of syphilis occurs most commonly during sexual intercourse, the majority of primary lesions appear on the genitalia or nearby structures. Extragenital chancres make up a small proportion of primary syphilitic lesions. Table VII in Chapter VI indicates the various sites at which extragenital chancres may be encountered as found in the Vanderbilt University Hospital Clinic, where they made up 5.5 per cent of all chancres, which is about the same as that found by other authors.

Occasionally children who are victims of sexual perverts develop an extragenital chancre as the first manifestation of the disease.

Patients who appear to have an uncomplicated urethritis may have an intra urethral chancre. The discharge being the sign of greatest importance to both the patient and the physician the presence of syphilis is obscured by the emergency at hand. It is well to keep the possibility of syphilis in mind. The patient should be examined, and blood tests should be made every two to three weeks for at least three months. This is

necessary since it has been shown that from 15 to 20 per cent of such patients become seropositive within that period

**Indirect contact** implies the transference of an infectious agent from one person to another as a result of contact with some inanimate object contaminated with the agent in question. In the transmission of syphilis by this means, the transference of the *T. pallidum* must take place quickly since the organism will die when dried. This inability of *T. pallidum* to withstand drying is a weakness which limits the transmission of syphilis by means of indirect contact, and protects exposed individuals.

Indirect transmission of syphilis occurs infrequently, but should be kept in mind. In some instances where this method of transmission occurs, chewing gum or premasticated food passed from an older person with acute syphilis to a child, are the vehicles of transmission. In a family epidemic reported by Gray and Cleveland, a 17-year-old white girl who had primary and secondary syphilis gave used chewing gum to two children, aged eight and four years, and a bolus of masticated food to a child two years of age. All three developed acute syphilis. The same authors cite another case in a child aged three years who acquired the infection from masticated food given it by the mother. The mother had secondary syphilis acquired from her husband, who had a chancre of the face. He had shaved with a razor immediately after it had been used by an individual who had had a chancre a short time before, and who at that time had a sore throat. Case 21 illustrates possible innocent syphilitic infection through a lesion due to other disease. In the cases of syphilis acquired through indirect transmission just cited, the contaminated article was passed quickly from one person to another.

**Prenatal transmission** of syphilis has been discussed in Chapters XIII and XIV. Mention is made of it again at this point only to emphasize its importance as a common method of infection.

The acquisition of syphilis by means of blood transfusion is a well-known method of transmission. This occurs only when the treponemata are in the blood stream (1) during the incubation period, (2) during the primary and secondary stages of the disease, (3) during the periods when infectious relapses appear, and (4) possibly during early latency. When syphilis is transmitted by transfusion, relatives or friends of the recipient usually have been the donors responsible for such accidental infections. It is possible to prevent cases of syphilis transmitted through blood transfusions by not only subjecting donors to routine testing of the blood, but by obtaining historical data with reference to recent exposure and previous treatment, and by performing a physical examination.

The source of danger in acquiring syphilis lies primarily in the acute infectious lesions in man himself or in materials shortly after their contact

with such lesions. Moist lesions and materials (such as dressings), and objects (such as pipes, cups, razors, and instruments) passed from person to person should be handled carefully.

The possibility of acquiring syphilis from females acting as passive carriers of *treponemata* has not been investigated carefully. The passive carrier implies the presence of organisms in the absence of acute infectious lesions. Under such conditions, women with latent syphilis or early syphilis under treatment, who are subjected to frequent sexual exposure, might have organisms deposited in the vagina and thus act as sources of infection.

Presumably every one is susceptible to syphilis. With advancing age susceptibility does not decrease, as for example in the case of diphtheria. Under suitable conditions of exposure, infants and aged persons acquire syphilis, which respects neither the social, economic, nor intelligence levels of individuals.

Not all persons infected develop clinical manifestations which are brought to the attention of physicians. It is estimated that at least one-third of the women and one-fifth of the men who acquire syphilis do not have recognized early clinical manifestations. Probably a high proportion of such individuals do have manifestations which are so mild or evanescent as to escape attention.

The immunologic aspects or host-parasite relationships of syphilis are not well defined. They have been briefly considered in Chapter II.

## CASE FINDING

In the preceding sections of this chapter the fundamental facts relative to the transmission of syphilis have been discussed. These facts can be applied by physicians and public-health workers in the prevention and control of syphilis. In addition to the technics and other procedures which will be described as case-finding measures, we would emphasize the importance of a sense of awareness of the magnitude of this medical problem, so that syphilis will be considered as a possible diagnosis in every patient who is seen by a physician.

Several procedures can be used in case finding: (1) history, (2) physical examination, (3) darkfield examination, (4) blood testing, and (5) investigation of contacts.

### HISTORY

When a history suggestive of syphilis is obtained, it may or may not mean that the patient actually has or has had the disease. When a positive history is obtained it is an indication for an intensive search for additional evidence. If additional evidence which corroborates the history is obtained,



the history may be considered to be significant. The absence of a history of syphilis does not exclude the disease because (1) a large proportion of patients give no history of syphilis, (2) insignificant lesions may be passed over as unimportant, (3) patients in the older age groups may forget significant historical data with the passage of time.

#### PHYSICAL EXAMINATION

Physical examination often reveals manifestations of the disease. However, in a majority of instances in clinic practice and in a high proportion of cases seen in private practice, the patient will present himself in the stage of latency in which the diagnosis is made on at least two positive blood tests. A complete physical examination should be done on every patient.

#### DARKFIELD EXAMINATION

The darkfield examination is extremely important in cases of primary, secondary, mucocutaneous relapse, and in other instances where lesions which are suggestive of syphilis are present. The application of this test makes it possible to diagnose syphilis much earlier. Thus, the patient is given a better chance for 'cure,' and the public is protected by rendering the patient noninfectious.

#### BLOOD TESTING

The blood test is the most efficient single test that can be applied for the diagnosis of syphilis. The necessity for accurate technic in the performance of such tests and the proper interpretation of them has been emphasized in Chapter IV. It is the only procedure by which the diagnosis can be made in latent syphilitic infection. With it, the physician has at his disposal a very efficient tool for the diagnosis of syphilis, providing he interprets the test accurately and has at least two positive tests on every patient before treatment is instituted.

Placing reliance on the blood test alone as a diagnostic procedure may lead the physician into error. In considering the disadvantages of blood testing as the only measure in the diagnosis of syphilis, the physician should remember that

- 1 The test may be negative in the early stages of the disease when a primary lesion is present. Serious consequences may occur in cases of primary syphilis in which a single test is negative early in the disease and the patient is told that he does not have syphilis.

- 2 In cases of late latent syphilis in which no treatment has been given the test may be negative.

- 3 In patients who have been inadequately treated, the blood test may be negative.

4 The blood test may be negative in cases in which neurosyphilis is present

5 In Chapter iv it has been emphasized that in certain diseases false-positive tests for syphilis have been found

6 Biologic false-positive tests are found in a small number of cases

7 False-positive tests may be the result of technical errors, or mistakes in labelling specimens or in reporting the results of the test

The measures which have been discussed are those which should be applied routinely in the case of any patient who presents himself to a physician for treatment or advice. It is only by carrying out such procedures and by the proper interpretation of the results that an accurate evaluation of the patient's status may be obtained

#### INVESTIGATION OF CONTACTS

The success of a syphilis-control programme depends to a large extent upon the discovery of those individuals who are transmitting the disease. This can be accomplished by means of the same procedures which are applied in other infectious diseases. The personnel of the health department should assume the responsibility for this activity since they are trained to conduct case finding investigations, and are accustomed to this type of work. Physicians in practice, however, should be interested in this important phase of the syphilis programme.

**Role of Practitioner** Practitioners hesitate to ask contacts of acute cases of syphilis to come to their offices for examination because of ethical considerations. However, physicians should assume the responsibility for securing the names of contacts of private patients, and for reporting them to the health department (by which agency they may be investigated as any other contact). This has been carried out successfully in Massachusetts and other places. If contacts of acute cases under the care of physicians are not reported, there is no other procedure by which such exposed persons may be advised and given the opportunity to have the proper examinations. Since physicians see in their private offices a majority of patients who have acute syphilis, the failure to report their contacts results in increasing the infectious reservoir of the disease and delays its control and prevention.

The epidemiologic approach strikes at the reservoir of infection. This reservoir includes patients who have primary or secondary lesions representing the initial attack of syphilis or individuals with relapse manifestations. In addition to these individuals, persons who are in the first two years of their syphilitic infection are considered to be potentially infectious since 85 per cent of the relapses occur within that period. In the present state of our knowledge every pregnant syphilitic woman should be

considered potentially infectious for her fetus. These women will be discovered usually by physicians in practice, or in clinics as a part of the routine prenatal examination. Therefore this phase of syphilis prevention is not the responsibility of the health department except when it conducts prenatal clinics or offers public-health nursing service in the home.

**Role of Public Health Departments** The case-finding programme of public-health departments is concerned mainly with contacts who have been exposed to persons comprising the groups enumerated above. With the immediate application of epidemiologic methods in every case of acute or early syphilis, exposed individuals may be brought under observation for a sufficient time to determine whether or not it is present at the time of examination, or whether it develops subsequently. For contacts of patients who present themselves with early latent syphilis, it is sufficient to secure two negative or two positive blood tests. However, for contacts exposed to primary or secondary syphilis, observation and frequent blood tests for a period of three months is necessary before such a contact can be reasonably certain that syphilis will not develop following the exposure.

The patient is the only person from whom the names of contacts may be obtained. Success or failure will depend upon the approach to the patient. The methods of approach which will be described are those which have been developed in the Vanderbilt University Hospital clinic during the past five years. The success in obtaining names of contacts depends upon the methods of approach and the attitude of the physician, social worker, or nurse who for the first time interviews the patient in order to obtain the names of contacts. This interview should be instructive as well as having the objective of getting information from the patient. A properly instructed patient will usually co-operate.

The following outline represents the points which are usually discussed with each new patient.

- 1 Syphilis as a communicable disease is interpreted to the patient. This includes such points as the nature of the disease, the modes of transmission, the possibility of spread from the patient to his associates, and instructions regarding the use of contaminated utensils. He is told to consult his physician as to when it is safe to resume sexual relations.

- 2 The possibilities of "cure" with regular treatment and the probabilities for the development of infectious relapse, neurosyphilis, and cardiovascular complications following irregular treatment are presented.

- 3 The patient is assured that the entire personnel of the clinic or health department are interested in his situation, and that everything will be done to help him. On the other hand, the patient is told he must assume some responsibility and make a conscientious effort to report regularly for treatment.

4 It is pointed out to the patient that he has an obligation to the community in the matter of assistance in the control of syphilis. The importance of finding exposed persons is explained, and the responsibility for giving identifying information regarding his contacts is placed upon the patient. He is also told that his name will not be revealed to the contact. This will usually result in the naming of contacts by the patient. It is not uncommon for the patient to name a contact from whom he suspects he has acquired syphilis. The interviewer should not agree with the patient, but should explain that all contacts should be named.

When the patients have primary syphilis, an attempt is made to obtain the names of all contacts during a period of three months prior to the onset of the initial lesion. In cases of secondary syphilis, the names of contacts during the six months preceding the onset of the disease are secured. If the patient has early latent syphilis, he is asked to name his contacts during the first two years of his infection, since during this period 85 per cent of relapses occur and such occurrences may not have been discovered.

5 The information obtained should be adequate to identify and find the person named. Such data as the name, approximate age, marital status, accurate address, a notation as to whether the contact lives with his family or not, are basic for any investigation of this kind. Other information as to frequency and date of last contact is important. Other data which may assist in identifying the contact are size, appearance, etc. The occupation and place of work are usually recorded. It is not our practice to visit contacts in their places of employment. It may be possible to reach them only by telephone after all other procedures have failed. It may require several conferences with the patient to obtain sufficient information to locate his contacts. It is not unusual for the patient to secure additional names if he is given time.

**Classification of Contacts** In our clinic the following classification of contacts is used: (1) *Sexual contacts*—(a) nonmarital, (b) marital, (2) *household*, and (3) *other*.

The terms "source" and "spread" contacts are not used as it is often impossible to state that the patient acquired his infection from a definite source. Frequently the patient thinks that he has transmitted syphilis to his contacts or acquired it from a certain person when upon investigation it is found that he and his contacts have acute syphilis acquired as a result of exposure to other persons. The above terms imply the placing of blame on others for the transmission of syphilis.

All persons who have been exposed to patients with infectious or potentially infectious syphilis and who are considered as contacts may be classified as follows: (1) *The independent single person*, (2) *the minor*

*living with his family*, or (3) *the married person*. This is a simple classification, making it possible to develop methods of approach for each group of contacts. These procedures can be used by all personnel responsible for investigation of contacts without much variation or deviation except when necessary in individual cases.

The procedures by which the epidemiologist, social worker, or public-health nurse may communicate with a contact are: (1) By personal interview with the contact, either in the field or in the clinic; (2) by personal letters; (3) by telephone; (4) by the patient bringing in his contacts; (5) by a combination of the above procedures: (a) *interviewing* contacts by visiting them has been found to be most satisfactory if field personnel are available. This permits both the investigator and the contact to establish a rapport which cannot be developed by any other method. It also makes it possible to explain syphilis as a disease and as a public-health problem. The investigator has an opportunity to "size up" the contact, and to determine what measures, in addition to the interview, may be necessary to get the contact examined. (b) *Letters* may be used to get in touch with contacts. However, they should be written so that they convey in a friendly manner the idea that the writer has a definite purpose in mind in asking the contact for an interview. Letters should be so composed that suspicion is not cast upon the person in the event that they fall into the hands of the spouse or members of the family of the contact. Failure to do this may lead to serious family difficulties which immediately prejudice the contact, preventing any action on his part. Often the first letters sent from health departments to contacts represent orders to report for examination rather than requests. Health departments do have the authority to examine persons suspected of having a communicable disease. In most cases, however, when they resort to police power for this purpose, they have failed in one of their many objectives; namely, public-health education. They may be successful in securing the examination, but they lose the willing co-operation of the patient.

In our clinic letters are used under the following circumstances: (1) After attempts have failed to secure an interview with the patient; (2) in circumstances where it is known that the contact will not be accessible for an interview at his residence because of his work schedule; (3) to communicate with exposed persons who cannot be reached by our own personnel, or by the members of a full-time health department; (4) in situations where it is urgent to communicate within a few hours with an exposed person. (We have found that a *registered special-delivery letter* will reach the individual promptly, and in many instances such a letter yields good results); (5) in circumstances in which the field staff of the clinic is reduced by vacations, illness, etc.

In areas where the health department has a minimum staff, letters to contacts may be the only routine procedure employed. Under such circumstances good results may be secured if attention is given to the necessary details.

(c) It is our practice to use the *telephone* to communicate with contacts at their places of employment only when we have failed to reach them by other means. When such calls are made, the contact is asked to come to the hospital to see the worker at an appointed time. The purpose of the interview is usually not given, but the request is made in such a manner as to indicate the urgency and necessity of complying with it. Often times the worker may leave only the telephone number and name if the contact himself is not reached by telephone. Employers as a rule do not wish routine work to be disturbed any longer than necessary, so that clarity and brevity in making such calls are essential.

(d) In some instances the patient refuses at the first interview to give the names of contacts, and states that he will bring them in or will advise them to go to a physician. In our experience this is unsatisfactory and should be discouraged, since patients who propose this often do not intend to co-operate. In most instances they tell the contact to "go and get a blood test" without explaining the reason for such a test at that time. This leads to confusion on the part of the contact and the epidemiologist as he does not know what has been said to the contact. When the investigator finally secures from the patient the name of the exposed person and interviews him, the contact already knows who "turned him in" and in many instances is prejudiced. Co-operation under these conditions may be very difficult to obtain.

Our practice is to discourage the patient in any effort he might make to bring in his contact unless he tells the exposed person all the facts and tells him that he, the patient, has been found to have "catching syphilis." Most patients will hesitate when confronted with such a proposal and a large proportion of patients will reply that they are unwilling to do that. This will result in the naming of contacts by many patients. Some patients, however, insist upon bringing their contacts in for examination and in some instances are successful. When the epidemiologist concurs in this plan he should have an agreement with the patient that if the contacts are not examined within a short time, usually one week, the patient will give their names to the investigator.

(e) While certain procedures are preferred, we do not wish to be dogmatic about any particular method. The method or methods used are adapted to each case. Some patients do not get on very well with a particular worker, and it becomes necessary to ask some one else to work out the problem with the patient. In this phase of syphilis control

those methods which can be employed best should be used after experience has shown which are more suitable in the various conditions under which they may be employed

In recent years certain developments have provided a means of discovering additional cases of syphilis. These are (1) required premarital blood tests, and (2) required prenatal blood tests in certain states and tests as a part of the pre-employment examination for industrial workers and food handlers. Prospective transfusion donors found to have positive tests should be investigated further.

Before discussing the methods of approach to the three groups of contacts as indicated previously, certain points should be emphasized: (1) The contact should be accurately identified, (2) the same methods should apply to all contacts, (3) the contacts should not be told from what source his name was secured, (4) the worker should not agree with the contact even though he may name the person who "turned him in" (The best reply to the question, "Who told you about me?" is—"If you turned some one in, would you want that person to know your name?" This reply usually appeals to an individual's sense of fairness, and the contacts usually are satisfied with it), (5) contacts should not be interviewed at their place of occupation, (6) even though minors who are sex contacts are easily accessible at school, they should never be interviewed there. Unpleasant situations may arise as the result of examining minors without the consent of their parents.

The above points are matters of general policy, and if followed will prevent many mistakes. It will enable the investigator to have a ready answer to some of the questions which contacts frequently ask. In the preceding and following discussions relative to methods of approach to contacts, the authors have used material published recently in an excellent paper by Anne Sweeney, of the Vanderbilt University Hospital Syphilis Clinic.

**THE INDEPENDENT SINGLE PERSON** In interviewing the independent single person it is well to spend a little time in becoming acquainted, so that any fear or suspicion that may be aroused as a consequence of the visit may be allayed. The contact is then told that it is our policy to notify persons who have been exposed to "catching" diseases such as tuberculosis and other conditions so that they may have an examination. In the case of the contact in question he is told that we have information that he has been exposed to "catching syphilis." All of the modes of transmission of the disease and the possibility of acquiring syphilis innocently are explained. He is told that, even though he may have no lesions at the time he is seen, they may develop later, or that, in some cases, syphilis may be acquired without the development of observed clinical

manifestations Late manifestations of syphilis are mentioned Emphasis is placed upon the fact that the only safe thing to do is to have a physical examination and blood tests made

The contact is then told that he can have his examination by his physician, in the local health-department clinics, in the clinics connected with the various hospitals, or in our own syphilis clinic. If he elects to go to his own physician, he is asked to name the doctor and tell us when he expects to go The physician named is notified so that he may know the circumstances and purposes for which the contact makes the visit *The physician is not given the name of the patient who named the contact* Our policy in keeping contacts of acute cases under observation for three months is explained during the conversation, and a request for a report of the results of the examination is made If the contact fails to see his doctor, additional visits are made If the contact refuses to report for examination, it is our policy to report him to the local health officer

The same procedures are followed with contacts who elect to go to health departments or other clinics If the contact comes to the Vanderbilt University Hospital, a careful inspection of the skin, mucous membranes, genitalia, perineum, and perianal region is made, and a specimen of blood secured If the diagnosis is established by darkfield examination or by two positive blood tests, the contact is placed under treatment If no evidence of syphilis is obtained after repeated observations, the contact is told that he probably does not have syphilis He is encouraged to return for observation at any time in the future if he wants advice, or if a skin rash or genital lesions develop Many contacts return with acute syphilis following subsequent exposure We believe that the education received while under observation for his previous exposure can be given the credit for the prompt placing of many cases under treatment under these circumstances

**THE MINOR LIVING WITH HIS FAMILY** The dependent minor living at home and named as a sexual contact should be approached in a manner different from that used in the case of the single independent person It should be emphasized that under such circumstances the minor must in most cases continue to live with and depend upon his family for support Any procedure which may disturb family relationships would undoubtedly prejudice the contact and his family This would defeat the purpose of the investigation In our clinic the procedure used is the "family approach" in which *all members of a family or household are considered to have been exposed to a patient with infectious syphilis* No implication is made to any member of the family that any one person in the household has been named as a contact This has the advantage of not pointing out any one individual It is our practice to examine household contacts as well as sexual contacts to acute syphilis so that the family approach has the added



objective of examining the other members at the same time. If the contact about whom the investigation centred is found to have syphilis, the other exposed persons have been examined. If after repeated observations the contact has not developed syphilis and the tests are negative on the other members of the family, the investigation is ended and those examined are told that syphilis did not occur following that exposure.

*This procedure has been satisfactory in our hands. The family relationships have not been disturbed. This type of approach allows the epidemiologist, social worker, or public-health nurse to talk to one or both parents depending upon circumstances at the first visit. The worker does not have to individualize the approach every time a problem of this kind arises. It precludes the dangers that may arise when the investigator tries to arrange an interview with the sexual contact who is a minor, either at school, in the factory, or in the health department. If a minor is found to have syphilis, the family ultimately will learn the facts and this usually leads to family disturbances. We have tried other methods but we have found that the "family approach" gives the best results.*

**THE MARRIED PERSON.** It is not unusual for married persons living with their spouses to be named as sexual contacts to acute cases of syphilis. Situations of this kind are handled on a "*family basis*," and all members of the family are examined. With such individuals *it is not our practice* to approach the contact in the same manner used in handling an independent single person. The advantages and disadvantages of this approach are essentially the same as those where we deal with the dependent minor who is a sex contact. In our hands the results with this method of approach have been satisfactory.

It should be pointed out that in cases where a husband or wife is seen with acute syphilis, it is not our policy to visit the spouse. After the patient has been instructed as to the nature of syphilis, the responsibility for informing the spouse is placed upon the patient. All possible aid is given to the infected person in interpreting the disease. Interviews are held with the spouse only upon the request of the patient, and with the understanding that the spouse will be given the same information which the patient has received. This policy has proved satisfactory in getting examinations made in circumstances of this kind.

**The Problem of Prostitution.** We feel that, in connection with the discussion of case finding, some statement relative to the question of prostitution should be made. It is recognized that all measures which have been used to control that group of people have been unsuccessful. The reasons for the failure are well known, and need not be presented again. The responsibility for the *suppression of prostitution* should be placed upon the *law-enforcement agencies* in a community. The responsi-

bility for the *control of infected persons and the investigation of their contacts* should be placed in the hands of the *health authorities* who are charged with the control of communicable diseases. The responsibility of each agency in regard to venereal diseases and prostitution is not clearly understood, as a rule, by either practitioners or general public.

The health department should treat infected prostitutes in the same manner as any other infected persons. It may be necessary to isolate them for a period of time sufficient to render them noninfectious, and there should be adequate facilities for this procedure. During the period of isolation, this group of persons if managed properly can be educated as to the necessity of voluntarily remaining under treatment following their release. It is obvious that not all such individuals will co-operate. In that circumstance enforced isolation should be carried out.

Contacts of prostitutes should be investigated by the same procedures used to find and place under treatment persons who have been exposed by the so-called nonprostitute group. This places the epidemiologic investigations of this problem on a uniform basis, and allows workers in this field to establish routine procedures which can be applied generally to most situations. The difficulties in obtaining from prostitutes the names of contacts are obvious. On the other hand, obtaining sufficient identifying information from persons whose infections are presumably acquired from prostitutes is difficult and at times impossible. If the contact occurred in a recognized house of prostitution, all persons connected with it may be investigated if the names of prostitutes are not known. The greatest difficulty arises when the exposure occurred as a result of a "pick-up" under diverse conditions in so-called taverns, roadhouses, etc.

The suppression of prostitution should be enforced in order to reduce the number of exposures. However, under normal circumstances such enforcement is a sporadic affair, and usually of short duration. Enforcement procedures should be on a community- or county-wide basis, and not directed at a few places. In our experience, unless this is done impartially it will fail in its purpose. This problem is important, but it should be borne in mind that the concentration of effort by public-health authorities against known prostitutes will not control or prevent venereal diseases since the problem involves the entire population.

The following examples of case investigations serve to illustrate the practical aspects of the various procedures which are used in the application of epidemiologic measures in early syphilis. Three of these studies were conducted as a part of the epidemiologic work in the Vanderbilt University Hospital Syphilis Clinic.

**Comment** This investigation was conducted following the examination of a young Negro male who was found to have secondary syphilis. In addition to



have syphilis, six of whom were in the infectious stage of the disease (Fig 85)

**Comment.** The first patient in this study was a white female who had a chancre of the breast acquired from nursing her child who had secondary lesions

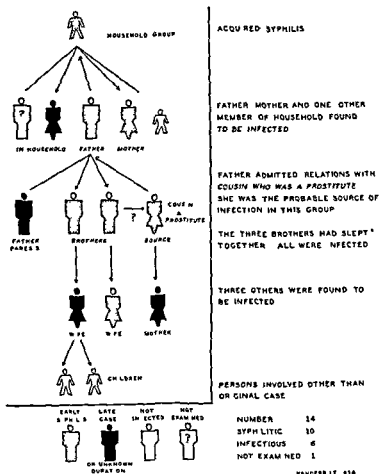
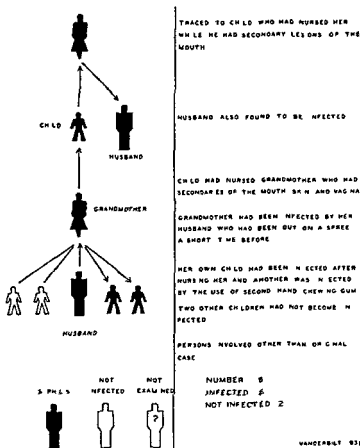


Fig 85 Investigation of contacts of infant with secondary syphilis (Arrows denote probable course of spread)

in the mouth Eight persons were studied, and six were found to have syphilis Of the six infected persons three were children with acute syphilis, two of whom had become infected through nursing and one had acquired the disease through secondhand chewing gum (Fig 86)

**Comment.** Figure 87 illustrates several important points The first case was that of a young white male who developed acute syphilis while he was a member of the Civilian Conservation Corps He was given a few injections of neoraspheamine and discharged from the C C C. He was told upon discharge to report to the County Health Officer, who would arrange for continuation of

his treatment. He failed to do this, developed an infectious relapse, and reported to a private physician for treatment. During his relapse he had sexual contact with three prostitutes, each of whom developed acute syphilis. The physician reported the original case to the health department. Subsequently the health

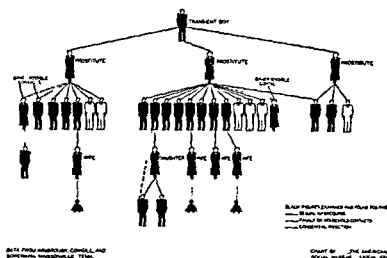


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FIG 86 Investigation of contacts of white female seen with chancre of breast (Arrows indicate probable direction of spread)

officers and the practitioner were able to examine thirty-six persons, thirty of whom were found to have syphilis. This study illustrates very well the dangers of inadequate treatment, the necessity of reporting promptly those acute cases who lapse treatment or who leave one area to reside in another place. It also shows that practising physicians can render valuable assistance in investigations of this kind.

The results of epidemiologic investigations conducted by Clark in our clinic are of interest in pointing out what can be accomplished when contacts



(Courtesy American Social Hygiene Association)

FIG 87 Outbreak of syphilis in a rural county (Monroe County, Tenn.)

of acquired syphilis are studied. In a series of 204 cases of primary or secondary syphilis, 387 sexual contacts were named. Of that number, 343 or 88.7 per cent were examined. Of the 343 sexual contacts examined, 258 or 75.3 per cent were found to have syphilis. In the latter group of 258 patients, 213 or 82.6 per cent were found to have infectious or potentially infectious syphilis. The group of 213 persons included 147 or 69.0 per cent patients with primary or secondary syphilis, 46 with early latent syphilis not previously diagnosed, and 20 patients with early latent infection previously diagnosed but inadequately treated. Thus, for each 100 original patients 104 additional patients capable of transmitting syphilis were brought under treatment as a result of the application of epidemiologic procedures.

It should be pointed out that in the course of investigation of sexual contacts additional patients who do not have infectious or potentially infectious syphilis may be found. Clark found that 45 or 13.3 per cent of the 258 contacts had late latent or late syphilis which had or had not been diagnosed previously.

In the investigation of contacts, more acute cases of syphilis will be discovered among sexual contacts than will be found among other groups of exposed persons. Only 15 per cent of 140 designated sexual contacts of 100 patients with early latent syphilis were found to be in the primary or secondary stage of their infections. Among 365 nonsexual family contacts of 520 patients with late latent or late syphilis, 10 cases of infectious or potentially infectious syphilis were found.

The above data are sufficient to show that the application of epidemiologic

logic methods in the prevention and control of syphilis is practical. The methods should be applied by official health agencies as a part of the programme for the prevention and control of communicable diseases. The medical and public-health personnel should be responsible for case investigation. If they are properly trained, tactful, and conscientious, there should be no more difficulty in conducting successfully a syphilis case-finding programme than there would be in the case of tuberculosis. The percentage of failures can be reduced to a low level, as shown in the unpublished data of Anne Sweeney in which 2,860 contacts were investigated over a period of two years. When the contacts were accessible, 93.3 per cent of nonmarital sexual contacts, 91.1 per cent of marital sexual contacts, and 88.5 per cent of household and other contacts were examined.

### CASE HOLDING

Keeping patients with syphilis under treatment, or case holding, is one of the important factors in the successful operation of a syphilis-control programme. Successful case holding is a good indication of the efficiency of those who deal with this problem. Patients seek medical treatment for syphilis (1) when they have clinical manifestations—such as primary, secondary, or late skin lesions, (2) upon finding that they have a positive blood test either during pregnancy or as a part of the routine physical examination, (3) when other manifestations, such as cardiovascular or central nervous-system symptoms are present, (4) following an interview or the receipt of a letter by which they have been informed that they are contacts, or (5) when in some instances they report voluntarily to their physician or to a clinic for a blood test.

If syphilis is found to be present the patient may indicate a sincere interest in his condition or may be sceptical about the diagnosis, especially in cases in which no lesions are present. When lesions are present the patient has visual evidence of a disease process which serves as an incentive to continue treatment. Even under such circumstances interest wanes when the lesions clear up. In our experience clinic attendance is more regular in the early weeks or months of treatment following which irregularities and lapses occur.

### REASONS GIVEN FOR PATIENTS' DELINQUENCY IN TREATMENT

The reasons given for delinquency in treatment are without limit. New excuses or reasons for not taking treatment regularly are brought in frequently. The following reasons are the most common ones, and they apply to patients treated in clinics or by private physicians. (1) The failure on the part of the first physician who examines the patient to give satisfactory instruction, (2) inability to get off from work, (3) transportation

difficulty, (4) lack of funds; (5) treatment reactions or difficulty in the treatment, (6) intercurrent illness in the patient or among members of his family or friends; (7) mismanagement of the patient, especially in public clinics, (8) interference or lack of interest by members of the patient's family, and (9) hesitancy in attending a public clinic

Frequently, the reason for lapse from treatment may be within the personality of the patient. The above reasons for clinic delinquency may be given by the patient to hide the real basic cause of his failure to attend clinic regularly, namely, irresponsibility, limited intelligence, etc. In clinics the personnel should recognize this type of patient, and should be prepared to deal with such problems on an individual basis

#### PROCEDURES INDUCING PATIENT CO-OPERATION

In our experience the following procedures are important in holding patients under treatment in clinics. Attention must be given to details in the following points which are obvious to the physician, but not practised often enough: (1) Individual patient education, (2) arranging convenient clinic hours, and the satisfactory adjustment of fees where clinic fees are collected. Private physicians should arrange the financial aspects of treatment so that the patient may remain under treatment for the proper period of time, (3) frequent observation and conferences with the patient, especially in the early weeks of his treatment experience, (4) a friendly attitude toward the patient on the part of all clinic personnel, (5) avoiding treatment reactions of all kinds, especially extravasation of trivalent arsenical drugs into the tissues, (6) assisting patients with any difficulties which may arise with employers, and (7) co-operation with physicians, other clinics, and agencies in behalf of the patient

Attention to the above points will result in obtaining good results in many instances with patients who would otherwise stop treatment. We do not wish to imply that these points represent the key to success in case holding in all patients. In every clinic there are some patients who will co-operate following a minimum of instruction and education. On the other hand, there are some who will fail to take treatment in spite of all the efforts that can be made. In a large proportion of patients, case holding must be secured through the observance of good clinic practice, and keeping in touch with the patient. The above principles are those which apply to the 'physician-patient' relationship as it occurs in the practice of medicine. If such principles are followed in all cases, a larger proportion of patients will receive more treatment than when attention is not given to them.



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## XVIII

# TREATMENT—A FACTOR IN THE PREVENTION AND CONTROL OF SYPHILIS

BY ALVIN E. KELLER, M.D.

FOR the control and prevention of syphilis, treatment of persons in the infectious or potentially infectious stage of the disease is necessary. Patients in the first two years of their infection are considered as potentially infectious because 85 per cent of the infectious relapses occur within that period.

It is not the policy of public-health administrators to treat diseased persons. However, when treatment is the only method by which a patient may be rendered noninfectious, it is considered as a function of the health department, which is responsible for the control and prevention of communicable diseases. Viewed in this light, treatment is an important element in the syphilis-control programme. The local medical society and the health officer should work out arrangements satisfactory to all concerned whereby antisyphilitic treatment may be administered in the health department. Such a procedure is necessary because a large segment of the syphilitic population will be unable to pay for treatment. In many instances treatment by private physicians is not available.

## OBJECTIVES

The objectives of treatment for syphilis may be considered first from the public-health point of view, and second from the social and economic aspects.

From the public-health point of view, treatment is the only method by which foci of infection may be sterilized and patients rendered noninfectious. This can be done more rapidly in the case of syphilis than in any other communicable disease, since within twenty-four hours from the time the first injection of a trivalent arsenical agent is given, a high proportion of darkfield-positive lesions are rendered negative.

A recurrence of infectious lesions may take place in a large number of cases under irregular or inadequate treatment. The characteristics of mucocutaneous relapses in syphilis have been described in Chapter VII. However, it is worthy of emphasis that infectious relapse lesions are especially likely to occur in the buccal mucous membranes and in the genital and perianal areas. These lesions which may appear to be insigni-

nificant are highly infectious because of the large numbers of organisms present

In the control of infectious syphilis certain points should always be kept in mind and emphasized to the patient if "cure" of the disease is to be secured and infectious relapse is to be prevented. These points are (1) Adequate dosage and number of injections of trivalent arsenic and bismuth, (2) regular treatment, (3) continuous treatment. Physicians have a large responsibility for the "cure" and prevention of infectious relapse. The institution of treatment in acute syphilis interferes with the development of immunity on the part of the host. Therefore, anything short of adequate treatment predisposes to subsequent infectious relapse. The relationship between the amount of treatment and infectious relapse depends mainly upon the number of doses of trivalent arsenical preparation which the patient receives. The Co-operative Clinical Group material, showing this relationship, was adapted by Clark as appears in Table LII.

TABLE LII

THE RELATIONSHIP OF INFECTIOUS RELAPSE TO THE AMOUNT OF  
TREATMENT RECEIVED

<i>Amount of Treatment</i>	<i>Per Cent Infectious Relapse</i>
1-5 injections of trivalent arsenical + 20 injections heavy metal	45
5-9 injections of trivalent arsenical + 20 injections heavy metal	9
Less than 20 injections of trivalent arsenical + 20 injections heavy metal	15
More than 20 injections of trivalent arsenical + 20 injections heavy metal	2

It is thus accepted that a minimum of twenty arsenical injections and twenty injections of a heavy metal is necessary to reduce infectious relapse to a minimum, though more than this amount is necessary to 'cure' the disease. It is not sound practice for health departments to discharge a patient from treatment after he has received twenty injections each of arsenic and bismuth. As shown in Chapter VIII, infectious relapse may occur even after ideal treatment. Physicians, patients, and the general public should not be led to have a false sense of security by stating that such an amount is sufficient.

The outlook of the patient is largely dependent upon the physician who first discovers his infection. The practitioner has the opportunity of "curing" more patients than can be "cured" in the clinic, because approximately 60 per cent of the patients with syphilis who seek medical service from physicians are in the acute stage of the disease. In the clinic the

figures are reversed. More patients with latent syphilis and late manifestations, some of which have had inadequate treatment previously, are admitted to clinics for diagnosis and treatment.

In addition to "curing" patients with acute syphilis, treatment is important in the prevention of infectious relapse, involvement of cardiovascular and central nervous system and late skin and bone lesions. With respect to congenital syphilis, treatment of syphilitic pregnant women is one of the most efficient preventive measures that can be employed in medical practice. If a pregnant syphilitic woman receives as many as ten injections of a trivalent arsenic agent and ten injections of bismuth before the fifth month of pregnancy, the child has better than a 90 per cent chance of escaping prenatal infection. The treatment in the stage of latency is essential for the prevention of the late manifestations mentioned above.

From the social and economic aspects, treatment is important in arresting the progress of central-nervous-system syphilis. This may prevent the patient from entering mental-disease hospitals, and in many instances may return patients to their former positions as productive workers. The direct and indirect costs of syphilis to the patient and general public are enormous when measured in terms of cost of treatment, loss of time from work, loss due to permanent or partial disability, loss from premature death, and the cost of aid to dependents of persons dying of syphilis.

Treatment of syphilis, though a therapeutic procedure, is one of the important measures in the programme for the prevention and control of syphilis as conducted by the health departments of the country. Health departments should assume the responsibility for (1) supplying the necessary therapeutic agents for patients who are to be treated in the physician's office, (2) providing accessible, properly equipped and staffed clinic facilities under the administrative control of the health departments, (3) providing for facilities for the follow-up of delinquent patients who are being treated in the public-health clinics or by private physicians, and (4) setting up a satisfactory reciprocal relationship with the public-health venereal-disease clinics of the country whereby the transfer of patients from one area to another can be effected with a minimum loss of time from treatment and observation.

A programme for the prevention and control of syphilis which does not provide the above procedures as an integral part will in all probability fail in the objectives for which it was planned. When the Kahn-Chamberlain Act authorizing the Division of Venereal Disease in the United States Public Health Service was passed in 1918, emphasis was not placed upon treatment by health departments. At that time education and assistance to physicians in the treatment of their patients were stressed. Since 1935,

however, treatment of syphilis has been emphasized along with epidemiologic and educational measures as one of the basic elements in the programme. Prior to 1935, only 20 to 30 per cent of all patients receiving antisyphilitic treatment received as many as twenty injections of an arsenical preparation and twenty injections of a heavy metal. If the present programme is to be effective, a majority of patients should be given adequate therapy.

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## XIX

### GENERAL EDUCATIONAL MEASURES IN THE PREVENTION AND CONTROL OF SYPHILIS

BY ALVIN E. KELLER, M.D.

EDUCATIONAL measures in the prevention and control of syphilis are applicable to the medical and allied professions, patients and contacts, and the general public. The "teaching of syphilis" is one part of the triad advocated by Parran for the control of the disease, namely, (1) find syphilis, (2) treat syphilis, (3) teach syphilis.

Until 1935 there was not a great deal of interest on the part of the medical profession in this problem. Prior to that time it was estimated that 66 per cent of the patients treated privately were treated by only 10 per cent of the physicians in practice, and that 25 per cent of patients were treated by 1 per cent of practising physicians. These data suggest that physicians were either not interested in the problem, were not prepared properly to treat the disease, or considered syphilis as a problem for the specialist.

Some physicians refuse to treat syphilis because of the alleged fact that other patients would not come to them if they are known to treat the disease. Other physicians feel that if they treat syphilis they will be considered "venereal-disease" specialists. Syphilis belongs to the field of internal medicine, and as such should be treated by general practitioners. This point of view should be emphasized, and patients educated to seek advice from their physicians, who have an excellent opportunity to be the first line of defence against syphilis. As was noted above, 60 per cent of infected persons seek the advice of their own doctors first. The physician in turn has an excellent opportunity either to treat them, or to refer them to proper treatment agencies.

#### EDUCATION OF MEDICAL AND ALLIED PROFESSIONS

Since the opening of the campaign against venereal diseases in 1935, provisions have been made for postgraduate education of physicians in this field. This has been carried out in the form of short courses given in certain medical schools designated by the United States Public Health Service. Physicians are selected by the state health officer, and while they are absent from their practices they receive a stipend from funds allocated to the states by the United States Public Health Service. Courses of this nature

have been of value to physicians, as is shown by a recent report by Frye, Kampmeier, and Keller, in which personal visits and interviews were made to physicians after they had attended such a course. For physicians in public health work, longer courses of instruction have been provided to allow for more extensive instruction and practical experience in syphilis control. In addition to short courses, the state health departments, together with the full time local health services, provide consultation for physicians in their cases. In some places physicians are afforded an opportunity to obtain instruction by participation in the syphilis programme of health departments while they continue in practice at home.

The medical schools of the country have always given some time to instruction of students in syphilis. In the light of the present knowledge of the magnitude and importance of syphilis as a medical and public health problem, the amount of time and the content of such instruction is not adequate. Every medical student should have an opportunity to participate in the work of a syphilis clinic conducted by a medical school. He should have experience not only in the treatment division, but should also be instructed in the diagnostic and epidemiologic aspects of the problem. To supplement the experience in the clinic, formal lectures which provide basic clinical and public health information should be given.

In addition to physicians and students of medicine, the instruction of undergraduate and postgraduate students in nursing has been rearranged and extended to include all of the points of view desirable for the training of nurses for routine hospital work, public health or industrial nursing services.

### EDUCATION OF PATIENTS AND CONTACTS

The education of the patient is of primary importance in the control of syphilis. The most opportune time to start the patient's education is when the diagnosis is made and the patient is told that he has syphilis. He will be found to be more receptive to advice and more willing to co-operate than at any other time. Time will be saved by arranging for the instruction of each patient to be informed relative to his problems at the beginning of treatment. This procedure is one of the best means of case holding, which is as important as case finding. During the early period of treatment, since patients are seen frequently, it may be possible to secure the names of contacts and to check on them between the patient's visits to the clinics.

In the Vanderbilt University Hospital Syphilis Clinic, each patient admitted with syphilis is instructed by the physician responsible for his treatment. The following paragraphs take up points which are discussed routinely.

In the education of the patient it is necessary to allay fear and correct any misinformation which he has acquired about syphilis. The disease should be interpreted in the present-day knowledge of the transmission of and the possibility of cure, especially in the acute stages. He should be told what constitutes adequate regular treatment, and what may happen if he is not co-operative. This places the responsibility for clinic attendance and for carrying out instructions on the patient.

The patient must be assured that proper protection will be afforded him in that his infection will not be divulged without his permission, but that all cases of venereal diseases are reported to the local health department. He is told that he will be expected to co-operate in his treatment, but that failure to do so will make his lapse from treatment necessary to be reported to the proper health authority. If legal steps should become necessary, the patient himself will be responsible for such action due to his failure to co-operate.

During the early periods of treatment, certain difficulties which may trouble the patient should be corrected. The most common obstacles to regular treatment of clinic patients are (1) lack of funds, and (2) difficulty in arranging for clinic attendance on a definite day each week. Most of these problems can usually be adjusted after a period of time.

The reason for securing the names of contacts is explained to the patient. At the same time, it is made clear that, in the approach to contacts, the patient's name will not be divulged, and therefore he should feel free to provide the name of his contacts. The patient thus is made to feel that he is taking part in a movement to assist in the control of syphilis, and has a sense of satisfaction in being of service to the community and his contacts.

There is no test which determines the intelligence of patients or the type and amount of education necessary for each patient. It is our practice to instruct each new patient in the clinic in the same manner. From experience it has been found that it may be necessary to instruct the same patient several times. On the other hand, some patients who in the first interview would seem to require a great deal of instruction co-operate much better than some who appear to need less education.

A co-operative spirit and relationship can be established in most instances by impressing on the patient the fact that his welfare is of the greatest importance to each person connected with the clinic, and that each person is anxious to help him. This relationship can be brought about by the proper handling of the patient outside of the treatment room. In addition to good technic in the administration of treatment, attention should be given to the complaints and questions which the patient may raise. Attention to such details will be reflected in better clinic attend-



ance and less delinquency, and will result in a reduction in the number of field visits necessary to hold patients under treatment. This statement is borne out by data which show that in a well-instructed group of patients, 80 per cent co-operated sufficiently to receive the minimum amount of treatment necessary to prevent infectious relapse, and that they attended the clinic 72 per cent of the time. In contrast to this, in a group of casually instructed patients only 54 per cent received as many as 20 injections each of an arsenical drug and heavy metal and attended the clinic only 62 per cent of the time.

## EDUCATION OF THE GENERAL PUBLIC

In presenting the subject of syphilis to the general public, it should be discussed as a communicable disease which can be controlled by medical and epidemiologic measures. There is sufficient information available with regard to syphilis to allow for a reduction in incidence of the disease in the population if these measures could be carried out. If the facts that are known are discussed clearly, there need be no discussion of "morals" and the "sinful" aspects of syphilis. The latter should be divorced entirely from any presentation by medical or public-health authorities. One of the reasons for the delay in the efforts to control syphilis has been the dilution of the energy expended on the programme by the inclusion of an attempt to improve the morals and social outlook of patients.

The education of the public is important in syphilis control, and should be conducted as a planned programme to reach all groups, especially those most likely to acquire the disease. The usual educational methods should be employed. The personal interview and discussion of the problem with individuals of various groups are advantageous under most situations because free discussion may be developed at the time the talk is given. Excellent motion pictures are available at present, and are suitable for use under the ordinary circumstance. Magazine and newspaper articles should be examined carefully for clarity and accuracy before they are recommended as educational material for the general public.

The attitude of the public at present is such that the subject of syphilis can be discussed openly and without apology. Material should be carefully selected in accordance with the group to be addressed, and it should be presented clearly. It is necessary that misinformation relative to syphilis be corrected. The public usually considers syphilis in the light of the old clinical descriptions—as a chronic disease with a protracted period of communicability, and which disabled a high proportion of its victims. Syphilis must be interpreted to the public in the light of present day knowledge, especially as to symptomless infections. Such points as the possibility of "cure," when treatment is begun early and continued regu-

larly, the possibility of the prevention of congenital syphilis, and the necessity for the treatment of syphilitic employees rather than their discharge, should be stressed

The programme of the official health department and co-operating agencies should be explained especially in relation to the local medical profession. The importance and possibilities of efficient contact investigation, the community facilities for clinic services, and the control of prenatal infection through efficient prenatal examination should be emphasized. An informed public will assume responsibility in regard to the provision of funds for the continuation and extension of the venereal-disease services in health departments.

There is a definite need for the development of a satisfactory method of reaching and teaching adolescents, but at present parents as a rule are not informed sufficiently to be able to give instructions to their children. As a result the responsibility is placed upon the school and health authorities. The response to such information on the part of high school students is usually good, but a great deal depends upon the group and the person giving the talk. In rural areas talks to school groups should be preceded by similar discussions before groups of parents so that they may know what will be presented to the children. Theoretically, it should not be necessary to separate male and female students, but this may be desirable in some communities to prevent criticism, and to allow freedom of discussion in the respective groups.

There are no satisfactory methods for providing sex education in the schools. This can be done best by parents. Children should be taught to consider the sex organs in the light of their proper function, and to consider them in the same light as they would the heart or the intestinal tract. It is necessary to answer questions correctly as they arise. Children will obtain information from improper sources if they are given incorrect answers, or if there is an attempt to delay an answer. Misinformation tends to discredit the informer in the eyes of the informant. The use of fear as an instrument to obtain sexual abstinence or proper sex behaviour is not effective. It is much more satisfactory to teach the advantages of sound healthy bodies, and to provide satisfactory recreational and social facilities under the guidance of directors in whom children have confidence. Under such conditions children will develop a great respect for each other, and their energies can be directed into proper channels.

The public should be taught to seek advice and treatment from physicians, and not from drug clerks, quacks, friends, and the so-called "venereal-disease specialist." This requires the co-operation of all groups concerned, especially those who dispense drugs. A study was conducted in 1939 by the American Social Hygiene Association for the purpose of

finding out what were the practices of clerks in drug stores with regard to the diagnosis and treatment of venereal diseases. In the study, 1,151 drug stores in thirty-five cities of twenty-nine states were canvassed. It was found that 62 per cent of the persons questioned in those establishments were willing to diagnose and sell remedies for venereal disease, 31 per cent were willing to diagnose, but not sell, only 7 per cent of them refused to diagnose or sell. A plan to improve such conditions is being developed whereby the American Pharmaceutical Association, the American Medical Association and the public-health agencies will co-operate to refer patients to ethical treatment agencies.

To determine what the man on the street knew with reference to treatment of venereal disease, a similar study showed the following. Of those questioned, 65.4 per cent advised a drugstore or self treatment, 31.4 per cent referred the inquirer to a physician or a clinic, and only 3.2 per cent replied that they did not know what to do. From these data it seems that a great deal of work remains to be done in the education of the public, especially among those groups in which there is greater need for protection and proper treatment. There must be a continuous educational effort, with adequate personnel and funds, if tangible results are to be obtained and if the campaign against syphilis is to succeed. If the syphilis-control programme is to succeed, there must be a continuous effort supported by adequate funds, public opinion, and co-operation of the medical profession.

### OBSTACLES TO EFFECTIVE CONTROL OF SYPHILIS

There are certain obstacles in the path of the effective control of syphilis. Among these is the failure on the part of physicians to assume responsibility for the treatment of patients or for the reference of patients to other treatment agencies. Furthermore, the failure to ask for consultation or to report contacts of early cases offers a great obstacle in the prevention and control of syphilis. The failure to recognize clinical syphilis and asymptomatic infections, and the failure to realize the importance of routine blood testing continues to add to the number of untreated patients and congenital syphilitics in the population.

The practice of affording symptomatic relief with a few doses of trivalent arsenic continues to add to the large reservoir of infection. The reliance placed upon serologic tests as a criterion for cure and upon the clinical appearance of a primary lesion for diagnosis contributes to delay in treatment and to missed cases. These factors together with the failure to use all available methods of diagnosis in early syphilis reduce the possibility of "cure" in a certain proportion of patients. Poor technique and obsolete methods discourage a great many patients, and account for delinquency in

treatment Spinal-fluid examination generally is neglected The practitioner is too often guided by the wishes of the patient in this regard, rather than by what is best for the patient This practice will continue to be responsible for the large number of patients who have late central-nervous-system sequelae Facilities for the control of syphilis are available readily to practically all physicians in the country The problem of syphilis is too large for any one medical group to handle alone If all the groups responsible for the treatment, prevention and control of this disease work together on the problem, there is no reason why the control of syphilis should not make great strides

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## THE INTENSIVE TREATMENT OF EARLY SYPHILIS

At the time of completion of the manuscript for this book, the intensive methods of applying arsenotherapy had been so recently applied that their evaluation, as regards results and hazards, was impossible. This was especially true in view of the avowed purposes of this volume, namely, a practical treatise for the general practitioner, health officer, and student. Therefore, the author felt that the introduction of such a controversial subject as intensive arsenotherapy would not be safe.

Now, at the time of a second printing (1944), a sufficient period of time has elapsed to permit a brief evaluation of the several methods of intensive arsenotherapy in early syphilis with respect to the results attained as well as to certain inherent dangers. I believe that on the side of conservatism it must still be emphasized that these methods are *experimental*. However, it also must be admitted that we surely are approaching the time when syphilologists will agree that the old method of thirty injections each of an arsenical preparation and bismuth will be outmoded. It seems certain that a shorter treatment scheme, probably consisting of multiple injections in a relative short time period, will be agreed upon and be recommended for use by the practitioner.

### DEVELOPMENT OF INTENSIVE TREATMENT METHODS

A brief summary concerning the background of the "short treatment" of syphilis should prove of interest.

Hyman and his collaborators, in studying the effect of the velocity at which intravenous injections of a variety of chemicals and drugs could be given, found that toxic materials could be safely administered by an intravenous drip. This suggested the possibility of giving neoarsphenamine in massive doses within a short time period in patients having early syphilis. Accordingly, in 1935, Chargin, Leifer, and Hyman reported the use of such treatment in twenty-five patients. These patients received an average of 4 Gm of neoarsphenamine in a five-day period. This paper indicated that the method was feasible, though no evaluation of the effect of treatment was possible at that early date. In 1939, these authors made a report on a five-year follow-up of some of the original group of twenty-five patients. Of fifteen patients observed for a sufficient period of time permitting an evaluation of treatment results, eleven remained seronegative and thirteen had normal spinal fluids. One patient undoubtedly, and another presumably, had been reinfectd.

As a result of this preliminary study the Commissioner of Health of New York City appointed a committee of syphilologists and internists in that city to supervise a continuation of the investigation at Mt Sinai Hospital. A second series of patients was treated, consisting of eighty-six males. Neoarsphenamine also was used in this group, in approximately the same dosage as in the first series of cases. A careful study was made of treatment reactions, arsenic excretion, and clinical and serologic results. The results seemed to indicate that they were as satisfactory as with accepted modes of prolonged continuous treatment. However, reactions such as toxicodermas and neuritides were troublesome.

During the period of experimental massive dose therapy with neoarsphenamine, arsenoxide (mapharsen) had been demonstrated to be an effective and relatively nontoxic drug. Therefore Hyman and his collaborators experimented with it in an effort to overcome the toxic reactions with neoarsphenamine. The adoption of arsenoxide eliminated the further use of neoarsphenamine in intensive treatment methods. In 1940, Hyman reported his preliminary results with this drug.

Because intravenous drip therapy required hospitalization, Thomas and Wexler at Bellevue Hospital in 1937 began to give first two and then three injections of arsenoxide weekly for four weeks in acute syphilis. This was followed by the usual routine treatment. In 1939, they began intensive treatment consisting of only two injections daily of arsenoxide for ten days. A total of 226 patients were treated in this fashion with an occurrence of three instances of hemorrhagic encephalitis—death occurred in two. In 1940, Schoch and Alexander began to use two injections daily, one-half hour apart, for ten days, in the treatment of acute syphilis.

Subsequent to this, other schemes of multiple injections developed. The major variation from the above methods of twice daily injections has been the development of thrice weekly injections for periods of four to ten weeks. The most extensive study of this plan of treatment has been going on since 1941 in a large group of collaborating clinics, the results being pooled and studied by Eagle.

Because of the effect of fever in altering host reaction to infection, it has also been introduced into intensive treatment schemes. Various students, including ourselves, have found hyperpyrexia alone to be inadequate in the production of "cure." Though lesions of acute syphilis respond to fever alone, there is subsequent relapse in a high percentage of cases. In the past several investigators have used fever therapy in conjunction with modifications of standard plans of chemotherapy. However, our interest at the moment is in the use of hyperpyrexia in intensive treatment methods for acute syphilis. Thomas and Wexler reported upon the use of fever produced by typhoid vaccine intravenously in addition to multiple injections

of arsenoxide In 1942, Simpson, Kendell, and Rose published the results of the combination of artificial fever and chemotherapy in the treatment of acute syphilis

### EXPERIMENTAL DATA

Experimental studies by Magnuson and Raulston indicate that following the giving of arsenoxide by the intravenous drip to dogs in doses of arsenic comparable to doses used in man, there is an increasing blood level of arsenic By the fourth day the level is twice that at the end of the first day (Probably the tissues become saturated and absorb less of the element ) Initially the major amount of arsenic is excreted via the liver in the bile, later excretion is mainly through the kidneys They point out there is an absence of serious tissue damage in spite of the large amount of arsenoxide used

Eagle and Hogan have studied the therapeutic efficacy of the intensive treatment methods as related to the margin of safety in experimental syphilis in rabbits They found no optimum method of treatment and stated that on any schedule of injections, whether weekly, tri weekly, daily, four times daily, or intravenous drip, any desired margin of safety between the tolerated dose and the therapeutic dose can be obtained by suitable prolongation of the time period of administration From the reports of intensive treatment schemes used in man Eagle and Hogan estimate that the curative dose of arsenoxide has been 20 to 30 mg per kg , or approximately 1500 mg in a man weighing 60 kg This has been independent of the frequency of injection or duration of treatment They believe this is in agreement with their experimental studies Their calculated margin of safety seems to be borne out clinically Thus the giving by intravenous drip of 1200 mg of arsenoxide resulted in a mortality of 1/200 and serious toxic reactions in 1/100 patients treated Routine weekly injections results in a mortality of less than 1/3000 These authors believe, from their calculations, that if the mortality from treatment is to be kept at less than 1/1000 persons treated, the treatment must take twenty days or more They feel a tri weekly schedule of treatment best meets this safety requirement as well as being more practicable for ambulant patients

### METHODS OF INTENSIVE TREATMENT

Since the intensive treatment of early syphilis is still in the experimental stage, no one scheme has crystallized out as that of preference It would be useless to outline all the variations of intensive treatment methods which have been advanced Only the ones will be outlined which have been used in fairly adequately sized groups of patients The technics will be briefly

described, and the results of treatment indicated in so far as this is possible at the present time. Unsatisfactory results in the reports on intensive therapy in acute syphilis indicate that one of the following occurred: (1) serologic fastness, (2) mucocutaneous relapse, or (3) serorelapse. For greater detail the reader must consult the original publications which appear in the references.



(1933 1941) is not detailed enough to be summarized in table form. Of 41 cases of *seronegative primary syphilis*, treated by drip with neoarsphenamine, small dosage of mapharsen (0.5-1 Gm.) or optimal dosage (1-2 Gm.), 39 or 95 per cent had a satisfactory course. Two had presumptive evidence that subsequent penile lesions represented reinfection. In their total of 382 cases of early syphilis, irrespective of type of drug used or its dosage, these authors felt that 81 per cent had a satisfactory course. If 15 retreatment cases are included the results were 88 per cent satisfactory.

Rattner's report in 1943 was based on the use of the intravenous drip of arsenoxide daily for five days in a total of 421 cases. Because of a rather high percentage of failures with arsenoxide alone, daily intramuscular injections of water-soluble bismuth were given for the five days in addition to the arsenic in 111 cases. Of 310 cases treated by arsenic alone, 200 were followed for five months or longer. Of these 86 per cent were classified as having had satisfactory results, 11.5 per cent as failures, and 2.5 per cent as pending. In the 111 cases having received both arsenic and bismuth in the five days of treatment, 76 were followed long enough for evaluation, the results were satisfactory in 93.5 per cent and failures occurred in 6.5 per cent.

Shaffer, who has used a "rapid drip" five-day treatment method, has treated 430 patients. He has had no failures in his seronegative primary cases. His expected failure rate in seropositive primary cases is 13 per cent and in secondary syphilis is 27 per cent. He has begun to use bismuth in conjunction with the five-day arsenotherapy in the hope of bettering his results.

#### MULTIPLE INJECTION METHODS

There are several methods in vogue. Presumably Thomas and Wexler were the first to use this method of intensive therapy in early syphilis, in 1939.

**Thomas and Wexler Plan.** Mapharsen was given twice daily, morning and evening, by syringe, each dose consisting of 0.06 Gm. in 10 cc. of distilled water. The course was completed in ten days. After some trial of this method they changed to a plan of giving 0.1 Gm. twice daily for six days.

**RESULTS.** These authors' results after a one-half to approximately four-year period of follow-up are as follows. In 153 patients treated with a dosage of 0.9 to 1.2 Gm., results are probably favourable in 81 per cent, in 122 treated with doses of 0.66-0.84 Gm., results are probably favourable in 75.3 per cent. The relapse or reinfection rate was 13 and 22.5 per cent respectively for these two groups.

Bundesen, Bauer, and Kendall used essentially the same plan in 200 patients. Infectious relapse or progression occurred in 5 per cent. The

question of ultimate serorelapse or serologic fastness could not be evaluated as yet from their reports

**Schoch and Alexander Plan** The plan was instituted in 1940 with the injection of 0.06 Gm of mapharsen in 10 cc of distilled water by syringe twice daily, the injections being given within thirty minutes of each other. The course was completed in ten days, a total of 1.2 Gm being given. After treating 208 patients, they modified the plan and treated 142 patients in a different fashion, though the details are not given. They merely say it is somewhat like the plan used in a few cases and described in their communication in 1941. This consisted of twenty injections of mapharsen in "full therapeutic dosage" over a period of four weeks.

**RESULTS** Of the 208 patients treated by the ten-day syringe method 103 were observed for from six to eighteen months. Therapeutic results were satisfactory in 77 per cent, failure was present in 12 per cent, and in 11 per cent the results were pending.

#### FEVER AND ARSENOTHERAPY

**"One-day Treatment" (Simpson)** Simpson and his associates treated twenty-three patients in the seropositive primary stage by this method. In one day the patient received a single ten-hour session of artificial fever at a temperature of 106° F, a dose of 0.25 Gm of bismuth subsalicylate in oil, and from 120 to 240 mg of arsenoxide. The latter was given in 0.06 Gm doses by syringe, every three hours, two to four injections being given.

**RESULTS** All twenty-three patients treated by Simpson became seronegative and results were satisfactory for the six months' follow up period concluded at the time of the report. With some slight modifications Simpson's plan has been used in Chicago as reported by Bundesen, Bauer, and Kendell. Among 774 patients treated there had been approximately 10 per cent of failures, and from the rising serologic titer in other cases it is apparent that the failure rate eventually may be higher.

**"One day Treatment" (Jones).** Jones and his collaborators have used a single fever session, the temperature being maintained at 106° F for a five-hour period, in conjunction with one of several methods of administering arsenoxide. Their treatment schedules have been (a) The injection of 1 mg of arsenoxide per kg of body weight during the time of fever induction before the temperature reaches 103° F, (b) the injection of this dose the night before the fever session, and a second dose of 1.5 mg per kg of body weight at the end of the hyperpyrexia, (c) the administration of 2 mg of arsenoxide per kg of body weight in a glucose-saline medium by intravenous drip at the termination of the fever session.

**RESULTS** The results reported by Jones and his group in acute syphilis

follow (The initial letter designates the treatment schedule described above )

(a) 72 cases followed six to twelve months, clinical relapse 18 per cent, serologic relapse 4 per cent

(b) 122 cases followed four to six months, clinical relapse 5.7 per cent, serologic relapse 0.8 per cent

(c) 86 cases followed zero to four months, clinical relapse 2.3 per cent, serologic relapse 0 per cent

Most of the infectious relapses have occurred within the first three months after treatment was completed, and the majority were in patients who had had secondary syphilis. Several probable reinfections were encountered.

**Thomas and Wexler Multiple Injection and Fever Plan** After these authors had treated 226 patients by the multiple syringe technic and had encountered several instances of hemorrhagic encephalitis, they modified the scheme. (Based on experiences of previous workers, there was reason to believe that fever enhances the therapeutic effect of smaller doses of arsenic and thus gives greater safety.) In their treatment scheme fever was induced by injections of typhoid vaccine intravenously, usually two injections (separated by two to three hours) were necessary to maintain a febrile level of 104° F or over for at least four hours. After a trial of treatment periods varying from seven to ten days, variable dosages of arsenoxide, and numbers of fever periods, the following plan has developed as described by these authors:

Day	Treatment*	
1	Arsenoxide	Bismuth salicylate
2	Arsenoxide	Typhoid vaccine { 0.1 cc. 0.1 cc
3	Arsenoxide	Bismuth salicylate
4	Arsenoxide	Typhoid vaccine { 0.2 cc 0.2 cc
5	Arsenoxide	
6	Arsenoxide	Typhoid vaccine { 0.4 cc 0.4 cc
7	Arsenoxide	Bismuth salicylate
8	Arsenoxide	Typhoid vaccine { 0.6 cc 0.6 cc.
9	Arsenoxide	
10	Arsenoxide	Bismuth salicylate

\* Arsenoxide is given in a dosage of 1 mg. per kg. of body weight. Bismuth salicylate in oil (100 mg.) is the heavy metal used. The typhoid vaccine used is the triple vaccine containing per cc. 1000 million typhoid organisms and 750 million each of paratyphoid A and B organisms.

**RESULTS** A total of 1022 patients were treated with arsenoxide combined with fever. Of this number of patients 700 were followed for from one half to three years. The treatment results in these cases are summarized in the accompanying table

<i>Number of Patients</i>	<i>Follow-up Time (in Mos)</i>	<i>Treatment Period (in Days)</i>	<i>Total Arsenoxide (in Gm)</i>	<i>Number of Fever Sessions</i>	<i>Percentage of Favourable Results</i>
256	6-38	7	0.6-0.8	3	78.5
88	6-35	8	0.84-0.9	2	86.3
356	6-38	10	0.5-0.7	4	80.3

#### LONG-TERM INTENSIVE THERAPY

The five-day treatment requires hospitalization and trained personnel for its administration. The multiple syringe method completing treatment within six to ten days is also probably safe only in a hospital. One-day treatment, employing one long term of fever and intensive arsenotherapy, requires hospitalization and trained personnel as much as does the five-day treatment. Furthermore, the hazards as shown in the deaths due to hemorrhagic encephalitis make necessary careful consideration when choosing certain of these methods of intensive antisyphilitic therapy. A careful selection of patients for such treatment and their close observation during and following treatment are prerequisites.

**Eagle's Plan** Because of these factors, and from his experimental studies (mentioned above) covering the margin of safety and therapeutic dose, Eagle was led to suggest the thrice-weekly injection of arsenoxide for varying periods of four, six, eight, and ten weeks. (The first two periods were abandoned quite soon because of unsatisfactory results.) Some patients have received one injection of bismuth in oil weekly, for comparison others have not.

The method consists of injections of arsenoxide three times a week with or without one weekly injection of 0.2 Gm of bismuth subsalicylate in oil intramuscularly. Dosage is estimated on a weight basis as follows

<i>Weight (in lbs)</i>	<i>Dosage of Arsenoxide (in mg)</i>
90	40
90-120	50
120-155	60
155-185	70
185	80

**RESULTS** Eagle has enlisted the co-operation of a large number of clinics throughout the country in applying this method. By adhering to

similar dosage and treatment schedules and by pooling results in Eagle's office, a large series of cases has been accumulated within a relatively short period of time. The results of this study have not been published. However, a preliminary report on the first 4,800 patients treated by this plan has been made available by Eagle.

It was found that the addition of a weekly injection of bismuth to the thrice-weekly injections of arsenoxide greatly increased the probability of cure. As a result Eagle feels that clinical and serologic cure may be anticipated in approximately 90 per cent of patients with acute syphilis by the use of his plan. The treatment period should be at least eight and probably ten weeks in length, during which tri weekly injections of arsenoxide and a weekly injection of bismuth salicylate are given.

**Army Plan.** A plan of treatment, representing a compromise between thrice-weekly injections and the standard prolonged treatment of early syphilis, has been in use by the United States Army for about two years. This plan of treatment is described on p. 155.

### UNTOWARD REACTIONS IN INTENSIVE TREATMENT

A variety of untoward reactions have been encountered in intensive treatment methods. Those associated with the use of neoarsphenamine are of little importance since this drug has no place in intensive treatment because of the necessarily greater amount of metallic arsenic involved in adequate dosage. For the same of brevity the incidence of untoward reactions has been tabulated as taken from the reports referred to in the bibliography. (See Table LIII.)

A number of other reactions have been mentioned, though not statistically, in several of the papers. Albuminuria and cylindruria occur, as evidence of renal irritation, not infrequently in the use of the five-day and multiple syringe methods. Acute nephrosis has occurred. Anaemia and blood dyscrasias have developed in some patients. Electrocardiographic changes have been found to develop during the five-day treatment. Arm pain has been noted in some patients. Headache, vertigo, and other central-nervous-system symptoms may occur aside from more serious features which indicate frank encephalopathy.

### SEROLOGY IN INTENSIVE THERAPY

In the studies which have been carried out in intensive arsenotherapy, quantitative tests have been used for the evaluation of the results of treatment upon the serologic tests for syphilis. This has been necessary so that the trend of reagin titer can be followed after treatment has been completed. Obviously, the seropositive case of early syphilis is certain to be still positive at the end of five days of treatment, whether by intravenous

drip or by multiple injection technic, or at the end of one day's treatment by fever and arsenotherapy. Only by the study of the downward trend in reagin titer in the weeks subsequent to treatment can therapeutic success be anticipated.

At this point it may be well to point out that in the intensive treatment of seropositive primary, of secondary, and of early latent syphilis seronegativity is attained in a period of time approximately the same as that in routine treatment. (Thus it is to be expected that the blood tests in seropositive acute syphilis will become negative in most instances within the first six months.)

It appears that if seronegativity is attained with intensive treatment it will be maintained in most cases. There have been some serorelapses, usually however with clinical relapse as well. (The experience of Thomas and Wexler has been that serologic relapse probably means clinical relapse.) Many cases at the time of their being reported were still listed as "pending," with titers either stationary or falling or rising. Whether the ultimate outcome will be in these can be determined only with the passage of time. In some series of cases apparent serologic-fastness occurred in from 10 to 15 per cent.

## RESULTS OF INTENSIVE TREATMENT

Unfortunately, at this time (in the middle of 1944), the end-results of intensive therapy methods cannot be accurately stated. Trends only can be indicated. As long as treatment methods have not become crystallized results are certain to vary. As was indicated above, in the discussion of methods, the students experimenting with intensive methods are constantly changing the dosage of arsenoxide, adding or varying accompanying bismuth therapy and fever sessions.

If failures of intensive therapy include serorelapse, mucocutaneous relapse, and serologic-fastness, the trend of the results in the intensive treatment of early syphilis is as follows:

In seronegative primary syphilis, cure in practically 100 per cent.

In seropositive early syphilis, satisfactory results in 75 to 85 per cent.

Comments were made above relative to the serologic response in short-term treatment. With regard to infectious relapse, figures have varied in several series from 4 to 5 per cent to about 10 per cent. Actually the relapse rate may not be this high. It is becoming apparent that reinfection is a greater possibility than was believed in the past. The authors reporting on intensive treatment methods have shown a laudable conservatism in classifying suspected reinfections as infectious relapse. Thus the incidence of relapse probably is being reported as higher than it actually is.

All papers on intensive treatment methods include re-treatment cases

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All papers on intensive treatment methods include re-treatment cases



TABLE LIII

FREQUENCY OF UNTOWARD REACTIONS (IN PERCENTAGES) OCCURRING DURING INTENSIVE TREATMENT

Treatment Plan	Num- ber of Cases	Fever		Dermatitis		Periph- eral Neu- ritis	Nausea and Vomiting	Jaun- dice	Cerebral Symptoms	
		Primary	Secondary	Mild	Severe				Total	Deaths
Leifer, et al Neosarsphenamine, 5 days	111	62.0	71.0	45.0	0.9	35.0	Frequent	3.6	1.8	1
Leifer, et al Mapharsen, 5 days	275	39.0	13.0	12.0		1.7		0.7	1.1	0
Rattner Mapharsen, 5 days	481	45.0	30.0	cases"	"Several		5.0	75.0	0.8	0
Schoch and Alexander Multiple syringe	350								0.8	1
Thomas and Wexler Multiple syringe	321	31.0	9.0	6.5		0.62		0.31	1.6	1

6.5% dis-  
continued

Thomas and Wexler Multiple syringe and fever	1,634	26.8	9.2	4.8	0.18	0.24	1.68	2	2 deaths in 588 treated in 78 days No death in 1,046 10-day treatments
<hr/>									
Bundesen, et al Multiple syringe	380			10.5			0.5	0	
<hr/>									
Bundesen, et al 1-day treatment	931								2 deaths 65 had to be removed from fever treatment
<hr/>									
Eagle Tri-weekly treatment	4,800		2.0		0.004	0.01	0.004	1	4 deaths

consisting of patients in whom the results were unsatisfactory and who were therefore given a second course of intensive treatment. The cases have been too few and have been followed too short a time to permit of the evaluation of second treatment courses.

In the relatively few results reported on spinal-fluid studies, it appears that invasion of the central nervous system is well controlled by the intensive treatment plans (Thomas and Wexler, for example, found only four instances of abnormal spinal fluid in 422 patients so examined six or more months after treatment. Furthermore, they encountered only one instance of neurorecurrence among 141 patients having relapse or reinfection).

Little has appeared in the literature regarding the results of intensive treatment in pregnant women. Rattner treated 27 such cases by the five-day plan. In all but one the pregnancy resulted in the birth of a full-term normal child. The one syphilitic child occurred in the case of a mother who had had one course of successful treatment and who acquired a second infection before the birth of the child. Furthermore, five women who had completed the five-day treatment and who subsequently became pregnant gave birth to normal infants even though no further treatment was taken. Thomas and Wexler mention in passing that they have treated 14 pregnant women with the fever and multiple injection technic. They merely say that fever had no untoward effects.

### SUMMARY

From the foregoing it is obvious that a great forward step has been taken in the development of methods of treating early syphilis short of 70 or more weeks of treatment—even though it may be said that such methods are still in the experimental stage. *These methods are applicable only to early syphilis*, that is, primary and secondary syphilis, and latent syphilis of probably no more than 12 months' duration.

As is to be expected, the methods have been applied to late syphilis, but only one or two papers have appeared on the subject and the results must be studied only over such long periods of time that it is useless to consider these now. In fact it seems as if, from a theoretical viewpoint, intensive therapy may not be applicable to the treatment of late syphilis, as stated by Moore and Mohr in commenting on intensive therapy and its possible effect in late syphilis. "It is generally thought that one reason for the less satisfactory curative results (in the biologic sense) of treatment in late as compared with that in early syphilis lies in the fact that in the late stages of the disease the organisms tend to localize in tissues which the relatively poorly diffusible trivalent arsenical drugs fail to reach in spirochetocidal concentration."

In early syphilis we may hope to attain approximately the same results by intensive treatment methods as by the older routine scheme. Admittedly this is done at a definitely greater hazard than with routine treatment.

Therefore Stokes, adopting a conservative attitude, pointed out in 1942 that in 4,841 cases treated by intensive therapy, hemorrhagic encephalitis led to death in one of every 220 cases, and to a nonfatal form in one of every 160 cases treated. He compares these rates with encephalopathy in one per 20,000 cases treated by conservative methods. Furthermore, with the use of arsenoxide in a conservative plan it would not even reach this figure. He states, "The general indications at this stage of development of intensive procedure are that the death rate will be from one hundred to two hundred times that of older, slower, but when effectively applied equally effective methods."

practitioner desires to *experiment* with some modification of intensive treatment he should limit himself to the use of Eagle's method of giving arsenoxide in the *advised dosage* thrice weekly and bismuth subsalicylate once weekly for *ten weeks*. He must insist on regularity of treatment, and must subsequently examine the spinal fluid as in any plan of treatment. Blood tests must be done every month for at least a year, and preferably longer. Examination for infectious relapse should be frequent and thorough. (Shaffer points out that in short treatment "the critical time for clinical or serologic relapse is between the third and ninth month and has usually been preceded by a dropping reagin titer to either negative or only slightly positive.")

In conclusion, it should be emphasized that intensive treatment of early syphilis is still *experimental*. (Its medicolegal status has not been tested to my knowledge.) It is to be used only in untreated syphilis of less than a year's duration. The physician should undertake intensive treatment only if he is willing and interested enough to follow the patient carefully by clinical examination and serologic tests. The only safe procedure for the practitioner in office or clinic practice is the plan of Eagle. Lastly, the final results of intensive treatment methods will become known only with the passage of future years.

## PENICILLIN

At the time of this writing it is too early to set down definite conclusions regarding the effectiveness of this substance as an antisypilitic agent. Its first use less than a year ago was noted on p. 81. The report, by Mahoney and his associates, covering the first four patients treated with penicillin, is still the only publication presenting details. However, at the 1944 Session of the American Medical Association,\* three papers were presented as *preliminary reports on the use of penicillin in the treatment of syphilis*.

The first of these three papers was presented by Mahoney, who reported that three of his original four patients had remained clinically and serologically well to date. The fourth patient was classified as an instance of clinical relapse, although reinfection was a possibility. This author has treated other patients since the first group of four. It was pointed out that it is too early to know what will be the ultimate outcome in these patients. However, serorelapse and seroresistance are being encountered.

Moore and others, representing a committee on penicillin therapy in syphilis, presented the preliminary results of treatment in *acute syphilis*. (This represents a collaborative study of pooled results of cases treated in a number of clinics. Penicillin for experimental use is supplied by the National Research Council. Vanderbilt University Hospital Syphilis Clinic

\* The three papers on the preliminary results of penicillin therapy will no doubt appear in the *Jour Amer Med Asso* in the summer or fall months of 1944.

is one of the clinics engaged in this study ) About 1,000 cases of acute syphilis have been treated and followed under this collaborative plan From Moore's preliminary report, the following broad statements may be made Penicillin is very effective in rendering the lesions of acute syphilis darkfield-negative within twenty-four hours Furthermore, it causes rapid healing (within a relatively few days) of the lesions of the primary and secondary stages The few cases of acute syphilitic meningitis which have been treated have responded satisfactorily There is a prompt downward trend of reagin titer in the blood (as determined by quantitative serologic tests), in most instances with eventual seronegativity Dosages of penicillin of a total of 600,000 units or less are associated with a high rate of clinical and serologic relapse This incidence of relapse or treatment-failure is much less with a dosage of 1,200,000 units However, Moore with laudable conservatism pointed out that the patients receiving the larger doses of the drug had been followed for fewer months than those with less dosage, and that the results were therefore still in the inconclusive stage This time factor is enhanced by the expected and necessary lag in reports from the collaborating clinics as stationary or apparently rising reagin titers are being checked at intervals

Stokes and others, representing the committee on penicillin therapy, reported preliminary results of the use of the drug in late syphilis The number of patients treated was much less than in the study of acute syphilis A variety of syphilitic manifestations have been treated Apparently late benign (gummatous) lesions responded satisfactorily to penicillin therapy The only other late manifestations of syphilis treated were instances of neurosyphilis (If one recalls the pathology and course of tabes dorsalis and general paresis, it is obvious that a study of such diseases, over a few months' time, can be said to be in a very early stage ) However, Stokes reported clinical improvement in some instances of early general paresis, as well as in tabes dorsalis In a fair percentage of instances there was an apparent downward trend in reagin titer in the spinal fluid with a decreased number of cells and flattening of the colloidal curve

From what has been said above, and as will appear in the papers referred to when they are published, the committee on penicillin therapy in syphilis has been extremely conservative in these preliminary reports It is obvious that it is too early to arrive at any conclusions as to the efficacy of penicillin in the treatment of syphilis In a year or two the status may be clarified However, it is apparent that an effective antispirechetal agent has been discovered which is nontoxic and which can be used in conjunction with arsenic Even at its worst, one may anticipate a valuable adjunct to intensive antisyphilitic treatment with arsenic and bismuth

For the practitioner it should be emphasized that penicillin as an anti-syphilitic agent is still in the *experimental stage*, and should be used only experimentally. It should be employed only with the knowledge that the ultimate relapse rate is not known as yet, which implies a most careful follow-up study of examinations for relapse lesions, quantitative serologic tests, and spinal-fluid examinations.

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